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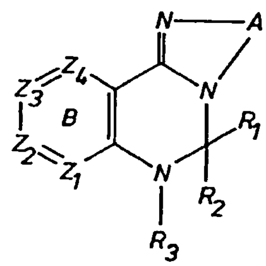
(54) **Polyazaheterocyclic compounds**

(57) Compounds of formula I



(I),

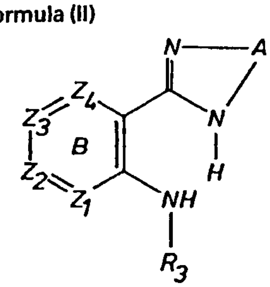
(R_1 and R_2 represent optionally substituted aliphatic hydrocarbon radicals, optionally substituted aryl or heteroaryl each having not more than 2 rings and each being bonded directly or via alkylene or alkenylene, R_3 represents hydrogen or alkyl,

A represents alkylene or alkenylene having 2 to 4 carbon atoms separating the nitrogen atoms,

and Z_1, Z_2, Z_3 and Z_4 represent radicals $-CH=$ carrying any substituents of ring B, one of which members can however also be the radical $-N=$, wherein R_1 and R_2 do not both represent methyl or ethyl if R_3 represents hydrogen, A represents ethenylene and ring B is unsubstituted

and their salts possess diuretic and antihypertensive activity and some of them are antidiabetically active.

The preparation of *starting materials* of formula (II)



is described.

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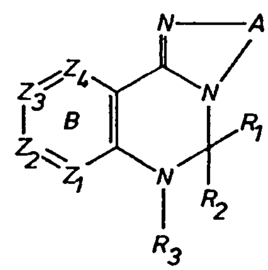
SPECIFICATION

Novel polyazaheterocyclic compounds, process for their manufacture and pharmaceutical preparations containing them

The present invention relates to novel polyazaheterocyclic compounds and their acid addition salts, a process for their manufacture and pharmaceutical preparations containing them, and also their use.

The compounds according to the invention correspond to the general formula



(I),

in which

R_1 and R_2 represent, independently of each other, optionally substituted lower aliphatic hydrocarbon radicals, optionally substituted aryl or heteroaryl each having not more than two rings and each being bonded directly or by way of lower alkylene or lower alkenylene,

R_3 represents hydrogen or lower alkyl,

and

A represents optionally branched lower alkylene or lower alkenylene having 2 to 4 carbon atoms in a direct chain between the adjacent nitrogen atoms,

and

Z_1, Z_2, Z_3 and Z_4 are members of the unsubstituted or substituted ring B and represent radicals −CH=, carrying the substituents of ring B, if such are present, one of which members can however also be the radical −N=, wherein R_1 and R_2 do not both represent methyl or both represent ethyl if R_3 represents hydrogen and A represents ethenylene and at the same time, the ring B is unsubstituted.

The invention relates also to the acid addition salts, especially the pharmaceutically acceptable acid addition salts, of the compounds of the general formula I.

In the compounds of the general formula I, the radicals designated "lower" contain, hereinbefore and hereinafter, unless stated otherwise, not more than 7, and preferably not more than 4, carbon atoms.

As lower aliphatic hydrocarbon radicals, R_1 and/or R_2 are lower alkyl, lower alkenyl or lower alkynyl. Lower alkyl R_1 and/or R_2 is, for example, pentyl, isopentyl, neopentyl, hexyl, isohexyl or heptyl, and preferably methyl, ethyl, propyl, isopropyl, butyl or isobutyl. R_1 and R_2 having that meaning contain together preferably at least 3 carbon atoms. Substituents of lower alkyl R_1 and/or R_2 are, for example, lower alkoxy or lower alkylthio, such as methoxy, ethoxy, propoxy, isopropoxy, butoxy or isobutoxy, and methylthio, ethylthio, propylthio, isopropylthio or butylthio, respectively, in any position, but preferably in the 2-position or a higher position, of the lower alkyl, or lower alkoxycarbonyl, such as methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl or butoxy carbonyl, in any position, but preferably in the 1-position, of the lower alkyl. As lower alkenyl, R_1 and/or R_2 is, for example, vinyl, 1-propenyl, allyl, 1-butenyl, 2-methyl-1-propenyl, 2-butenyl, 2-methylallyl, 1-pentenyl, 3-methyl-1-butenyl, 3-methyl-2-butenyl, 3,3-dimethyl-1-butenyl, 1-hexenyl or 1-heptenyl and, as lower alkynyl, is, for example, 2-propynyl or 2-butynyl, which can likewise be substituted in the manner mentioned above for lower alkyl.

As an aryl or heteroaryl radical having not more than 2 rings, R_1 is, for example, phenyl, 1- or 2-naphthyl, 5-membered heteroaryl, for example furyl, such as 2- or 3-furyl, thienyl, such as 2- or 3-thienyl, pyrrolyl, such as pyrrol-2-yl or pyrrol-3-yl, pyrazolyl, such as pyrazol-3-yl, pyrazol-4-yl or pyrazol-5-yl, isoxazolyl, such as 3-, 4- or 5-isoxazolyl, isothiazolyl, such as 3-, 4- or 5-isothiazolyl, oxazolyl, such as 2-, 4- or 5-oxazolyl, thiazolyl, such as 2-, 4- or 5-thiazolyl, 6-membered diazaheteroaryl, for example 3-pyridazinyl, pyrimidinyl, such as 2-, 4- or 5- pyrimidinyl, 2-pyrazinyl, benzoheteroaryl, for example indolyl, such as 2-, 3- or *ar*-indolyl, quinolinyl, such as 2-, 3-, 4- or *ar*-quinolinyl, phthalazinyl, such as 1- or *ar*-phthalazinyl, quinoxalinyl, such as 2- or *ar*-quinoxalinyl; quinazolinyl, such as 2-, 4- or *ar*-quinazolinyl, or especially pyridyl, such as 2-, 3- and more especially 4-pyridyl. All of these radicals can be bonded either by way of lower alkylene, for example propylene, trimethylene, tetramethylene, 1-methyl- or 2-methyl-trimethylene or especially ethylene or methylene, or by way of lower alkenylene, such as propenylene, 1-methylethenylene and especially ethenylene (vinylene), or especially directly.

As substituents of aryl or heteroaryl R_1 and/or R_2 there come into consideration, for example, lower alkyl, such as ethyl, propyl, isopropyl, butyl, isobutyl, tert.-butyl and especially methyl; lower alkoxy, such as ethoxy, propoxy, isopropoxy, butoxy, isobutoxy and especially methoxy; lower alkylthio, such as ethylthio, propylthio, isopropylthio, butylthio and especially methylthio; halogen, especially halogen having an atomic number of not more than 35, i.e. fluorine, bromine and especially chlorine; trifluoromethyl, methylenedioxy,

hydroxy, sulphamoyl, nitro, or amino optionally mono- or di-substituted by lower alkyl, or amino substituted by lower alkylene or 3-oxa-1,5-lower alkylene, such as methyl-, ethyl-, propyl-, isopropyl-, butyl- or isobutyl-amino, dimethyl- or diethyl-amino; or 1-pyrrolidinyl, piperidino or morpholino. One or more, but preferably not more than three, such substituents can be present and, in the latter case, can be identical or different, wherein, however, not more than two hydroxy or optionally substituted amino groups can be present and, preferably, as with methylenedioxy also, not more than one such group can be present, and not more than two alkylthio or trifluoromethyl groups can be present, and preferably not more than three of each of the other substituents can be present.

R_3 as lower alkyl is, for example, propyl, butyl, isobutyl, pentyl, isopentyl, neopentyl, hexyl, heptyl and especially methyl or ethyl.

As optionally branched lower alkylene or lower alkenylene having two carbon atoms in a direct chain between the two nitrogen atoms, A is respectively, for example, propylene (1-methylethylene), 1,1-dimethylethylene, 1,2-dimethylethylene, 1-ethylethylene and especially ethylene, and 1-methylethenylene, 1,2-dimethylethenylene and especially ethenylene (vinylene). Radicals A according to the definition having three carbon atoms between the two nitrogen atoms are, for example, 1-methyl- or 2-methyl-trimethylene, 1,2-dimethyl- or 1,3-dimethyl-trimethylene, 1,1- or 2,2-dimethyltrimethylene, 2- or 3-methylpropenylene, 2,3- or 3,3-dimethylpropenylene and especially trimethylene or propenylene, and radicals A according to the definition having 4 carbon atoms between the two nitrogen atoms are, for example, 1- or 2-methyltetramethylene, 1,1- or 2,2-dimethyltetramethylene, 1,4- or 2,3-dimethyltetramethylene, 1,1- or 2,3-dimethyl-2-butenylene and especially tetramethylene or 2-butenylene.

As substituents of the ring B or of its ring members Z_1 to Z_4 as $-CH=$, the same as those in aryl or hetero-aryl R_1, substantially also in the same number, can be present, there coming especially into consideration, in addition to the unsubstituted ring B, especially rings B that are substituted up to three times, but more especially once, by lower alkyl, especially methyl, by lower alkoxy, especially methoxy, and/or by halogen having an atomic number of up to 35, especially chlorine, and also rings B that are mono-substituted also by other substituents among those mentioned for aryl or heteroaryl R_1.

As acid addition salts, especially pharmaceutically acceptable acid addition salts, of the compounds of the general formula I there come into consideration, for example, those with suitable inorganic acids, such as hydrohalic acids, for example hydrochloric acid or hydrobromic acid, and nitric acid, sulphuric acid or phosphoric acid, or those with suitable organic acids, such as organic carboxylic acids, *inter alia* optionally hydroxy-containing lower alkane- or lower alkene-carboxylic acids, for example acetic acid, propionic acid, glycolic acid, succinic acid, maleic acid, hydroxymaleic acid, methylmaleic acid, fumaric acid, malic acid, tartaric acid or citric acid, or aryl-, aryl-lower alkane-, aryl-lower alkene- or heterocyclyl-carboxylic acids, for example benzoic acid, cinnamic acid, mandelic acid, salicylic acid, 4-aminosalicylic acid, 2-phenoxybenzoic acid, 2-acetoxybenzoic acid, embonic acid, nicotinic acid or isonicotinic acid, or organic sulphonic acids, such as optionally hydroxy-containing lower alkane-sulphonic acids, for example methanesulphonic acid, ethanesulphonic acid, 2-hydroxyethanesulphonic acid or ethane-1,2-disulphonic acid, or arylsulphonic acids, for example benzenesulphonic acid, 4-methylbenzenesulphonic acid or naphthalene-2-sulphonic acid, or other acidic substances, such as ascorbic acid. Corresponding to the close relationship between the free bases and their acid addition salts, hereinafter, where appropriate, information concerning free bases relates also to acid addition salts and, conversely, information concerning acid addition salts relates also to free bases.

The novel polyazaheterocyclic compounds of the general formula I and their addition salts with inorganic and organic acids possess valuable pharmacological properties. In particular, they have a diuretic and natriuretic action on rats in a dosage range of from 10 to 1000 mg/kg *per os* and on dogs in a dosage range of from 5 to 50 mg/kg *per os*, as can be ascertained by collecting the urine for three hours after administration (rats) and hourly for 5 hours after administration (dogs) and determining the urine volume and the sodium, potassium and chlorine ions. In this connection, the compounds of the formula I are distinguished by the absence of any influence on the eliminations of potassium, and their good tolerability also should be pointed out. Especially pronounced is the diuretic activity in the case of those compounds of the general formula I in which A represents optionally branched lower alkylene having 4, or especially 3, carbon atoms in a direct chain between the adjacent nitrogen atoms, especially trimethylene. Accordingly, the compounds of the general formula I, especially those of the kind mentioned above, and their pharmaceutically acceptable acid addition salts can be used as potassium-neutral diuretics and anti-hypertensives for the treatment of edematons states and hypertension.

Those compounds of the general formula I in which the radical A has two carbon atoms in a direct chain between the two nitrogen atoms also possess hypoglycaemic activity, as can be demonstrated in normal-metabolism rats after oral administration of doses starting from 3 mg/kg, and also in rats in which a diabetes-like metabolic state has been induced by injecting streptozotocin [cf. A. Junod *et al.*, Proc. Soc. Exp. Biol. Med. *126*, 201-205 (1967)]. In contrast, their diuretic activity is less pronounced. The reduction in the blood sugar level is accompanied neither by hyperlactacidaemia nor, in normally fed rats, by an increase in plasma-insulin. The pharmacological findings characterise such compounds of the general formula I and their pharmaceutically acceptable acid addition salts as anti-diabetics that can be used for the oral treatment of hyperglycaemia in mammals, especially for the treatment of *diabetes mellitus*.

The compounds of the general formula I possess, in addition, anti-phlogistic and anti-nociceptive activity,

which can be demonstrated in the case of oral administration in the kaolin-oedema test on the rat paw and in the writhing syndrome test on mice. They also have a lipid-reducing action, as can be detected, for example, in male rats in the case of administration of 50 mg/kg each day for three successive days and 50 mg/kg twice on the fourth day, by the reduction in the very-low-density lipoproteins (= VLDL) and in the triglycerides in the serum obtained on the fifth day.

The invention relates especially to polyazaheterocyclic compounds of the general formula I in which R_1 and R_2 represent radicals corresponding to the definition given under formula I which are unsubstituted or substituted in the manner stated in detail above, and together and including the optionally present substituents have preferably 3 to 20 carbon atoms and especially 5 to 15 carbon atoms, wherein R_1 and R_2, as aryl, represent especially phenyl and, as heteroaryl, represent especially pyridyl, thienyl or furyl, which radicals are unsubstituted or substituted as stated above, R_3 represents hydrogen, or lower alkyl having not more than 4 carbon atoms, and A represents unsubstituted ethylene, trimethylene, ethenylene, propenylene or tetramethylene, or ethylene, trimethylene, ethenylene, propenylene or tetramethylene substituted by lower alkyl, especially by one or two methyl groups, wherein substituted ethylene and trimethylene have respectively not more than 4 and 5 carbon atoms, the radicals Z_1, Z_2, Z_3 and Z_4 have the meanings given under formula I, and the ring B is unsubstituted or substituted in the manner stated in detail further above, and the acid addition salts thereof, especially the pharmaceutically acceptable acid addition salts thereof.

The invention relates more especially to compounds of the general formula I in which R_1 represents mono-heterocyclic mono-cyclic heteroaryl which is unsubstituted or substituted by lower alkyl, lower alkoxy and/or halogen having an atomic number of up to 35 and is bonded by way of methylene or, preferably, directly, especially unsubstituted pyridyl or pyridyl correspondingly substituted, especially by lower alkyl, such as methyl, or correspondingly substituted or especially unsubstituted thienyl or furyl, R_2 represents just such a radical, especially unsubstituted or correspondingly substituted pyridyl, or correspondingly substituted or especially unsubstituted thienyl, or unsubstituted phenyl or phenyl substituted as stated above for mono-cyclic heteroaryl R_1, or unsubstituted lower alkyl or lower alkyl substituted as stated further above, especially unsubstituted lower alkyl or lower alkoxycarbonyl-lower alkyl, especially lower alkoxycarbonylmethyl, R_3 represents hydrogen or alkyl having not more than 4 carbon atoms, especially methyl or ethyl, and A represents ethylene or trimethylene, the radicals Z_1, Z_2, Z_3 and Z_4 have the meanings given under formula I and the ring B is substituted in the manner stated in detail above for R_1, especially, however, by halogen having an atomic number of up to 35, such as chlorine, especially at the Z_2 ring member, or is especially unsubstituted, and the acid addition salts thereof, especially the pharmaceutically acceptable acid addition salts thereof.

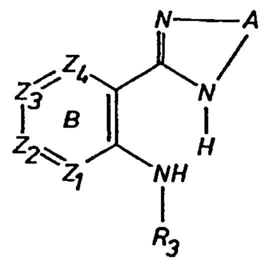
The invention relates most especially to compounds of the general formula I in which R_1 represents unsubstituted pyridyl or pyridyl substituted by lower alkyl, especially methyl, or thienyl, especially 2-thienyl, R_2 represents just such a radical or phenyl substituted by lower alkyl, lower alkoxy or halogen having an atomic number of up to 35, or especially unsubstituted phenyl, lower alkyl or lower alkoxycarbonyl-lower alkyl, especially lower alkoxycarbonyl-methyl, R_3 represents hydrogen or lower alkyl, especially methyl or ethyl, A represents ethylene or trimethylene, Z_1, Z_2, Z_3 and Z_4 represent radicals $-CH=$, Z_2 of which can be substituted by halogen having an atomic number of up to 35, especially chlorine, and, hence, the ring B is unsubstituted or correspondingly substituted, and the pharmaceutically acceptable acid addition salts thereof.

Compounds of the last-mentioned type in which A represents ethylene are, for example, those mentioned below which, in the case of oral administration to rats of the dosages each indicated in mg/kg in parenthesis, bring about a reduction in the blood sugar level of at least 20 %: 5-methyl-5-(4-pyridyl)-2,3,5,6-tetrahydro-imidazo[1,2-c]-quinazoline (10), 5-methyl-5-(6-methyl-2-pyridyl-2,3,5,6-tetrahydro-imidazo[1,2-c]quinazoline (3), 5-butyl-5-(4-pyridyl)-2,3,5,6-tetrahydro-imidazo[1,2-c]quinazoline (10), 5-methyl-5-(2-pyridyl)-8-chloro-2,3,5,6-tetrahydro-imidazo-[1,2-c]quinazoline (3), 5-phenyl-5-(4-pyridyl)-2,3,5,6-tetrahydro-imidazo[1,2-c]quinazoline (10), and 5-(4-pyridyl)-2,3,5,6-tetrahydro-imidazo[1,2-c]quinazoline-5-acetic acid ethyl ester (10), and 5-propyl-5-(4-pyridyl)-2,3,5,6-tetrahydro-imidazo[1,2-c]quinazoline (3).

Compounds of the last-mentioned type in which A represents trimethylene are, for example, those mentioned below which, in bitches (number of animals = n) in a dosage of 20 mg/kg *per os* produce, in the first 5 hours after administration, the following average hourly elimination of sodium, potassium and chlorine ions and urine volume (= vol.), expressed as a percentage of the amounts excreted from the same animals in the hour immediately before administration: 6-phenyl-6-(4-pyridyl)-3,4,6,7-tetrahydro-2H-pyrimido[1,2-c]quinazoline ($n = 4$, Na^+ 1224, K^+ 114, Cl^- 1369, vol. 409); 6-phenyl-6-(2-pyridyl)-3,4,6,7-tetrahydro-2H-pyrimido[1,2-c]quinazoline ($n = 2$, Na^+ 392. K^+ 56, Cl^- 308, vol. 171); 6-(4-methylphenyl)-6-(4-pyridyl)-3,4,6,7-tetrahydro-2H-pyrimido[1,2-c]quinazoline methanesulphonate ($n = 2$, Na^+ 800, K^+ 103, Cl^- 850, vol. 206); 6-(4-chlorophenyl)-6-(4-pyridyl)-3,4,6,7-tetrahydro-2H-pyrimido[1,2-c]quinazoline ($n = 4$, Na^+ 1673, K^+ 92, Cl^- 868, vol. 301); 6-(4-pyridyl)-6-(2-thienyl)-3,4,6,7-tetrahydro-2H-pyrimido[1,2-c]quinazoline ($n = 4$, Na^+ 1738, K^+ 100, Cl^- 1233, vol. 514); 7-ethyl-6-phenyl-6-(4-pyridyl)-3,4,6,7-tetrahydro-2H-pyrimido[1,2-c]quinazoline fumarate (1:1) ($n = 4$, Na^+ 721, K^+ 66, Cl^- 889, vol. 275). In the case of the first-mentioned compound, the excretions within the first 5 hours after administration of 20 mg/kg *per os*, as a percentage of the excretions of 10 untreated control animals, determined simultaneously for the same period, were for Na^+ 2263, K^+ 137, Cl^- 751 and vol. 379. All the above tests show, on the one hand, the sharp increase in the excretion of sodium and chlorine and also the increase in the urine volume, whereas, on the other hand, the

elimination of potassium is unchanged or, in part, even decreased.

The compounds of the general formula I and their acid addition salts can be manufactured in a manner known *per se*, for example by condensing a compound of the general formula II



(II)

in which R_3, Z_1, Z_2, Z_3, Z_4 and A have the meanings given under formula I and the ring B, as stated there, can be substituted, or an acid addition salt of the same, with a ketone of the general formula III

$$R_1 - CO - R_2 \qquad \text{(III)}$$

in which R_1 and R_2 have the meanings given under formula I, or a reactive functional derivative of the same, if desired introducing lower alkyl as the radical R_3 into a compound of the general formula I in which R_3 represents hydrogen, and/or converting a resulting compound of the general formula I into an acid addition salt or liberating the compound of the general formula I from a resulting acid addition salt.

The condensation of a compound of the general formula II with a ketone of the general formula III or a reactive functional derivative thereof can be carried out, for example, in the presence of an inert organic solvent, for example in a lower alkanol, such as methanol, ethanol, isopropanol or butanol, in an aromatic hydrocarbon, such as benzene, toluene or a xylene or xylene mixture, or in an N-substituted acid amide, such as dimethylformamide or hexamethylphosphoric acid triamide, for example at temperatures between approximately 0° and approximately 180°C, preferably at room temperature to approximately 150°C and preferably in the presence of an acid or an acid catalyst. As the acid there may be used, for example, a mineral acid, such as hydrogen chloride or concentrated hydrochloric acid, preferably in a lower alkanol, also polyphosphoric acid, for example in dimethylformamide or as the sole reaction medium, or a catalytic amount of an arenesulphonic acid, such as *p*-toluenesulphonic acid, preferably in an aromatic hydrocarbon, such as toluene, especially at the boiling temperature thereof, while removing the water liberated by azeotropic distillation. As acid catalysts there come into consideration, for example, strongly acidic ion-exchange resins, such as, for example, Amberbite IR 120 $H^{\oplus}$– form (trade mark of Rohm & Haas Co., Philadelphia, U.S.A.). Instead of acid catalysts, other agents that promote the liberation of water can also be used, such as silica gel or aluminium oxide, and the condensation can in turn be carried out preferably in a solvent that renders possible the removal of the water liberated by azeotropic distillation in a water separator, such as, for example, in toluene at the boiling temperature thereof. Also polyphosphate ester (PPE) may be used.

The reaction can alternatively be carried out in the absence of solvents or diluents, but preferably at elevated temperatures between approximately 120 and 200°C and likewise in the presence of acids or acid condensation agents, such as, for example, a catalytic amount of *p*-toluenesulphonic acid, or a preferably at least equimolar amount of aluminium chloride to which a solid diluent, such as sodium chloride can have been added. As will be apparent from the above and from the Examples, the reaction conditions can vary within wide limits. Clearly, more energetic conditions than are necessary for achieving as complete a reaction as possible are not used. Within the scope of the above-mentioned range, relatively energetic reactions conditions are generally necessary if directly bonded cyclic radicals are present as R_1 and R_2 in the starting materials of the general formula III employed.

As reactive functional derivatives of ketones of the general formula III there can be used, for example, alcoholates, such as lower alkanolates, ketals, such as dimethyl, diethyl and ethylene ketals, or oximes and imines.

The introduction of lower alkyl in place of a hydrogen atom R_3 can be effected in a manner known *per se*, for example by reacting a compound of the general formula I containing a hydrogen atom as R_3 with a reactive ester of a lower alkanol, especially a corresponding hydrohalic acid ester, lower alkanesulphonic acid ester or arenesulphonic acid ester, more especially a lower alkyl halide, especially iodide or bromide, such as, for example, methyl or ethyl iodide, or propyl or butyl bromide, in the presence or absence of an organic solvent, for example a lower alkanol, such as methanol, ethanol or isopropanol, a lower alkanone, such as acetone or 2-butanone, a lower alkanoic acid ester or amide, such as ethyl acetate or dimethylformamide, or a low-boiling hydrocarbon or polyhalohydrocarbon, such as benzene, toluene or methylene chloride, and an acid-binding agent, for example an alkali metal compound, such as sodium hydride, or sodium or lithium amide, a tertiary organic base, such as triethylamine or ethyldiisopropylamine,

or an inorganic base, such as potassium or sodium carbonate, preferably at temperatures between 0°C and 120°C and, if necessary, in a closed vessel, especially, however, at room temperature to the boiling temperature of the reaction mixture.

Of the starting materials of the general formula II, some representatives are known and others can be manufactured analogously to the known compounds. For example, they can be obtained by a reaction sequence described in US-PS 3 920 687 for the manufacture of 2-(2-aminophenyl)-4,5-dihydro-1H-imidazole and 2-(2-aminophenyl)-4,5-dihydro-5,5-dimethyl-1H-imidazole and in US-PS 3 922 282 for the manufacture of 2-(2-amino-4-chlorophenyl)-4,5-dihydro-1H-imidazole, which, for the mentioned compounds, comprises the N-acylation of anthranilic acid methyl ester and 4-chloroanthranilic acid methyl ester, respectively, with p-methoxy-benzenesulphonyl chloride, boiling of the resulting N-(*p*-methoxybenzenesulphonyl) derivatives with 1,2-ethanediamine and 2-methyl-1,2-propanediamine, respectively, and heating of the resulting derivatives of 4,5-dihydro-1H-imidazole with 92 % sulphuric acid and freeing of the desired process products with excess aqueous ammonia solution. The 2-(2-aminophenyl)-4,5-dihydro-1H-imidazole was also manufactured according to Zh.Prikl.Khim. *43*, 1641 (1970) (cf. Chem. Abstr. *73*, 77138r) by condensation of anthranilic acid with 1,2-ethanediamine in the presence of a certain cation-exchange resin at room temperature, and according to J. Med. Chem. *13*, 697 (1970) by catalytic hydrogenation of 4,5-dihydro-2-(2-nitrophenyl)-1H-imidazole or 2-(2-nitrophenyl)-1H-imidazole; cf., in connection with the latter, also Il Farmaco, Ed. Sc. *30*, 536-546, especially 539 (1975). A further process that comes into consideration is, for example, the condensation of unsubstituted or ring-substituted 2-aminobenzonitriles, or of corresponding aminopyridinecarbonitriles having an amino and a cyano group at adjacent ring carbon atoms, with optionally C-lower alkylated 1,2-ethanediamine. As compounds of the general formula II having lower alkyl as R_3, the 4,5-dihydro-2-[2-(methylamino)-phenyl]-1H-imidazole and the 4,5-dihydro-2-[2-(ethylamino)-phenyl]-1H-imidazole were manufactured according to Bull. Soc. Chim. France 1975, 2118-20 by reacting the corresponding 1-lower alkyl-1,2-dihydro-3,1-benzothiazine-4-thiones with 1,2-ethanediamine in a boiling mixture of ethanol/benzene (2:1).

As starting materials of the general formula II in which the radical A contains respectively three and four carbon atoms in a direct chain between the two nitrogen atoms, 2-(2-aminophenyl)-1,4,5,6-tetrahydropyrimidine and 2-(2-aminophenyl)-1,5,6,7-tetrahydro-1H-1,3-diazepine, respectively, have been described by Russell Kwok in J. Heterocyclic Chem. *15*, 877-880 (1978). Other compounds of that type can be manufactured analogously to the process described in that work, i.e. by heating for several hours optionally ring-substituted 2-aminobenzonitrile with approximately half the molar quantity, in each case, of optionally C-lower alkylated 1,3-propanediamine or 1,4-butanediamine, and the bis-4-methylbenzenesulphonates thereof at approximately 200°C. Furthermore, corresponding starting materials can also be obtained, for example, by heating an optionally ring-substituted 2-aminobenzonitrile, or a corresponding aminopyridinecarbonitrile having an amino and a cyano group at adjacent ring carbon atoms, with approximately double the molar amount of optionally C-lower alkylated 1,3-propanediamine and a little carbon disulphide at approximately 120 to 170°C for some time, for example approximately 2 to 48 hours, while stirring and passing nitrogen through the mixture.

Of the ketones of the general formula III, some are known and others can be manufactured analogously to the known ketones: lower alkyl pyridyl ketones, for example, by reacting the corresponding pyridinecarbonitriles with lower alkylmagnesium halides according to Grignard.

Depending on the process conditions and the starting materials, the novel compounds are obtained in free form or in the form of their salts which is likewise included in the scope of the invention, it being possible for the novel compounds or salts thereof also to be in the form of hemi-, mono-, sesqui- or poly-hydrates thereof. Salts of the novel compounds can be converted into the free compounds in a manner known *per se*, for example by treatment with basic agents, such as alkali metal hydroxides, carbonates or bi-carbonates, or ion-exchangers. On the other hand, resulting free compounds can form acid addition salts in a manner known *per se*, for example by treatment with organic or inorganic acids, such as the acids mentioned above, there being used for the manufacture especially those acids which are suitable for the formation of pharmaceutically acceptable salts.

These or other acid addition salts of the novel compounds, such as, for example, oxalates, picrates or perchlorates, can also be used for purifying the resulting free bases by converting the free compounds into salts, separating and purifying these and liberating the bases from the salts again.

Depending on the starting materials and procedures chosen, the novel compounds can be in the form of racemates or optical antipodes or, if they contain at least two centres of asymmetry, also in the form of mixtures of racemates. The starting materials can also be used in the form of certain optical antipodes.

Mixtures of racemates can be separated into the racemates according to methods known *per se*, especially by means of physical separating processes, such as fractional adsorption and elution, including chromatography, fractional crystallisation and distillation, etc..

Racemates can be separated into the antipodes according to methods known *per se*, for example by recrystallisation from an optically active solvent, by treatment with suitable micro-organisms or by reaction with an optically active compound that forms a salt with the racemic compound, especially a corresponding acid, and separation of the salt mixture obtainable in that manner, for example on the basis of differing solubility, into the diastereoisomeric salts, from which the free antipodes can be liberated by the action of suitable agents. Especially customary as optically active acids are, for example, the D- and L-forms of tartaric

acid, bis-O,O'-(*p*-toluoyl)-tartaric acid, malic acid, mandelic acid, camphorsulphonic acid, glutamic acid, aspartic acid or quinic acid. Advantageously, the more active of the two antipodes is isolated.

The invention relates also to those forms of the process according to which a compound obtainable as an intermediate at any stage of the process is used as starting material and the remaining process steps are carried out, or the process is discontinued at any stage, or in which a starting material is formed under the reaction conditions, or in which the reactants are optionally in the form of their salts.

For carrying out the reactions according to the invention there are advantageously used those starting materials which result in the groups of end products given special mention at the beginning and in the end products described or emphasised, for example in the Examples.

The starting materials are known or, if they are novel, can be manufactured according to methods known *per se*, as described above, for example in a manner analogous to that described in the Examples. The invention relates also to novel starting materials. The invention relates also to intermediates that can be obtained in accordance with the process.

The novel compounds can be used, for example, in the form of pharmaceutical preparations which contain a pharmacologically effective amount of the active substance, optionally together with inorganic or organic, solid or liquid, pharmaceutically acceptable carriers and which are suitable for enteral, for example oral, administration or parenteral administration. Thus, tablets or gelatine capsules are used which contain the active substance together with diluents, for example lactose, dextrose, sucrose, mannitol, sorbitol, cellulose and/or glycine, and/or lubricants, for example siliceous earth, talc, stearic acid or salts thereof, such as magnesium or calcium stearate, and/or polyethylene glycol. Tablets can also contain binders, for example magnesium aluminium silicate, starches, such as maize, wheat, rice or arrowroot starch, gelatine, tragacanth, methylcellulose, sodium carboxymethylcellulose and/or polyvinylpyrrolidone, and, if desired, disintegrators, for example starches, agar, alginic acid or salts thereof, such as sodium alginate, and/or effervescent mixtures, of adsorption agents, colouring substances, flavouring substances and sweeteners. Furthermore, the novel pharmacologically active compounds can be used in the form of parenterally administrable preparations or in the form of infusion solutions. Such solutions are preferably isotonic aqueous solutions or suspensions, it being possible to manufacture these before use, for example in the case of lyophilised preparations which contain the active substance on its own or together with a carrier, for example mannitol. The pharmaceutical preparations can be sterilised and/or contain adjuncts, for example preservatives, stabilisers, wetting agents and/or emulsifiers, solubilisers, salts for regulating the osmotic pressure and/or buffers. The present pharmaceutical preparations, which, if desired, can contain other pharmacologically active substances, are manufactured in a manner known *per se*, for example by means of conventional mixing, granulating, coating, dissolving or lyophilising processes and contain approximately from 0.1 % to 100 %, especially from approximately 1 % to approximately 50 %, and, in the case of lyophilisates, up to 100 %, of the active substance.

The novel compounds of the general formula I and their pharmaceutically acceptable acid addition salts are preferably administered perorally. The daily doses vary between 0.5 and 30 mg/kg for mammals and, for mammals weighing approximately 70 kg, are preferably between 50 and 1000 mg, especially between 100 and 500 mg depending on the individual condition and age. Corresponding oral unit dose forms, for example dragées or tablets or capsules, contain preferably from 25 to 500 mg, especially from 50 to 250 mg, of an active substance according to the invention, i.e. a compound of the general formula I or a pharmaceutically acceptable acid addition salt thereof, together with pharmaceutical carriers.

The following prescribed method is intended to explain the manufacture of tablets in detail:

a) 500 g of 5-propyl-5-(4-pyridyl)-2,3,5,6-tetrahydro-imidazo[1,2-c]quinazoline are mixed with 500 g of lactose and 340 g of potato starch, the mixture is moistened with an alcoholic solution of 10 g of gelatine and granulated by passing it through a sieve. After drying, 60 g of potato starch, 60 g of talc, 10 g of magnesium stearate and 20 g of highly disperse silica are mixed in and the mixture is pressed to form 10,000 tablets each weighing 150 mg and containing 50 mg of active substance, which can, if desired, be provided with dividing grooves for finer adjustment of the dosage.

Instead of the above-mentioned active substance, it is also possible to use, for example, 500.0 g of 5-phenyl-5-(4-pyridyl)-3,4,6,7-tetrahydro-2H-pyrimido[1,2-c]quinazoline, its methanesulphonate, its acetate dihydrate or another pharmaceutically acceptable acid addition salt thereof.

The following Examples illustrate in detail the manufacture of the novel compounds of the general formula I and of the starting materials that were not known hitherto, but are not intended to limit the scope of the invention in any way. The temperatures are given in degrees Centigrade.

Example 1

12.11 g (0.1 mol) of methyl 4-pyridyl ketone [cf. J. Med. Chem. *14*, 551 (1971)] are added at 0° to a solution of 8.06 g (0.05 mol) of 2-(2-aminophenyl)-4,5-dihydro-1H-imidazole (cf. US-PS 3 920 687) in 125 ml of 1.8 N methanolic hydrogen chloride solution. The reaction mixture is stirred at room temperature for 60 hours and is then evaporated to dryness *in vacuo*. 125 ml of 1N sodium hydroxide solution are added to the residue and the mixture is extracted several times with chloroform. The combined chloroform phases, washed neutral with water and dried over sodium sulphate, are concentrated by evaporation and the residue is recrystallised from isopropanol. The resulting 5-methyl-5-(4-pyridyl)-2,3,5,6-tetrahydro-imidazo[1,2-c]quinazoline melts at 227-228°.

Analogously, using 12.11 g (0.1 mol) of methyl 3-pyridyl ketone [cf. Liebigs Ann. Chem. *486*, 95 (1931)], 5-methyl-5-(3-pyridyl)-2,3,5,6-tetrahydro-imidazo[1,2-c]-quinazoline having a melting point of 170-171° (from ethanol/ether) is obtained; and, using 12.11 g (0.1 mol) of methyl 2-pyridyl ketone [cf. J. Med. Chem. *14*, 551 (1971)], 5-methyl-5-(2-pyridyl)-2,3,5,6-tetrahydro-imidazo[1,2-c]-quinazoline having a melting point of 202-203° (from ethanol/ether) is obtained.

The starting material, 2-(2-aminophenyl)-4,5-dihydro-1H-imidazole, can also be obtained, more simply than as described in US-PS 3 920 687, in the following manner:

a) A mixture of 118.14 g (1 mol) of 2-aminobenzonitrile, 120.2 g (2 mol) of ethylenediamine and 0.5 ml of carbon disulphide is heated at 150°C for 16 hours while stirring and introducing nitrogen, during which ammonia is evolved. The reaction mixture is then concentrated by evaporation *in vacuo*, the residue is taken up in hot ethyl acetate with the addition of active carbon, the mixture is filtered and hexane is added to the filtrate while stirring vigorously. Upon cooling, 2-(2-aminophenyl)-4,5-dihydro-1H-imidazole crystallises out, m.p. 60-64°. After recrystallisation from ether/hexane, the product melts at 63-64°.

Example 2

A solution of 8.06 g (0.05 mol) of 2-(2-aminophenyl)-4,5-dihydro-1H-imidazole, 12.11 g (0.1 mol) of methyl 4-pyridyl ketone and 0.8 g (0.0042 mol) of *p*-toluene-sulphonic acid monohydrate in 200 ml of toluene is boiled under reflux for 15 hours with water being separated. The mixture is cooled, the precipitate that has formed is filtered off and partitioned between 1N sodium hydroxide solution and methylene chloride. The methylene chloride phase, washed neutral with water and dried over sodium sulphate, is concentrated by evaporation. The 5-methyl-5-(4-pyridyl)-2,3,5,6-tetrahydro-imidazo[1,2-c]quinazoline obtained after recrystallisation of the residue from isopropanol melts at 228 - 229°.

Example 3

Analogously to Example 1, starting from 8.06 g (0.05 mol) of 2-(2-aminophenyl)-4,5-dihydro-1H-imidazole, 12.68 g (0.085 mol) of propyl 4-pyridyl ketone [cf. J. Chem. Soc. (C) 1969, 2134] and 200 ml of 1.8N methanolic hydrogen chloride solution, 5-propyl-5-(4-pyridyl)-2,3,5,6-tetrahydro-imidazo[1,2-c]quinazoline having a melting point of 241 - 242° (from isopropanol/ethyl acetate) is obtained.

Example 4

Analogously to Example 1, starting from 8.06 g (0.05 mol) of 2-(2-aminophenyl)-4,5-dihydro-1H-imidazole, 8.81 g (0.08 mol) of 2-furyl methyl ketone [cf. Helv. Chim. Acta *13*, 356 (1930)] and 150 ml of 1.8N methanolic hydrogen chloride solution, 5-methyl-5-(2-furyl)-2,3,5,6-tetrahydro-imidazo[1,2-c]quinazoline having a melting point of 195 - 196° (from ethanol) is obtained.

Example 5

Analogously to Example 1, 8.06 g (0.05 mol) of 2-(2-aminophenyl)-4,5-dihydro-1H-imidazole are reacted with 20.22 g (0.1 mol) of 3-oxoglutaric acid diethyl ester in 240 ml of 1.8N methanolic hydrogen chloride solution. The resulting, crude 5,5-bis-(ethoxycarbonylmethyl)-2,3,5,6-tetrahydro-imidazo[1,2-c]quinazoline is dissolved in 2.1N ethanolic hydrochloric acid. The hydrochloride is precipitated by adding ether. It melts at 213 - 214°.

Example 6

12.11 g (0.1 mol) of methyl 4-pyridyl ketone are added at 0° to a solution of 9.78 g (0.05 mol) of 2-(2-amino-4-chlorophenyl)-4,5-dihydro-1H-imidazole (cf. US-PS 3 922 282) in 160 ml of 2.5N methanolic hydrogen chloride solution. The reaction mixture is boiled under reflux for 15 hours and then concentrated *in vacuo*. After the addition of ether, a precipitate of the mono- or di-hydrochloride or 5-methyl-5-(4-pyridyl)-8-chloro-2,3,5,6-tetrahydro-imidazo[1,2-c]quinazoline forms which is filtered off and partitioned between 1N sodium hydroxide solution and chloroform. The organic phase is washed neutral with water, dried over sodium sulphate and concentrated by evaporation. Recrystallisation of the residue from acetonitrile/isopropanol yields 5-methyl-5-(4-pyridyl)-8-chloro-2,3,5,6-tetrahydro-imidazo[1,2-c]quinazoline having a melting point of 242 - 244°.

Analogously, using 12.11 g (0.1 mol) of methyl 2-pyridyl ketone, 5-methyl-5-(2-pyridyl)-8-chloro-2,3,5,6-tetrahydro-imidazo[1,2-c]quinazoline having a melting point of 247 - 249° (from ethanol) is obtained.

Example 7

8.06 g (0.05 mol) of 2-(2-aminophenyl)-4,5-dihydro-1H-imidazole and 10.63 g (0.055 mol) of β-oxo-4-pyridinepropionic acid ethyl ester [cf. J. Am. Chem. Soc. *67*, 1468 (1945)] are heated in 80 ml of 2.1N ethanolic hydrogen chloride solution for 15 hours at 90° in a closed vessel. The reaction mixture is evaporated to dryness and the residue is partitioned between 2N sodium hydroxide solution and chloroform. The organic phase, washed neutral with water and dried over sodium sulphate, is concentrated by evaporation. The residue is filtered with a mixture of chloroform:methanol:concentrated ammonia = 150:50:1 over silica gel having a particle size of 0.063 - 0.200 mm. The fractions containing the desired product are concentrated by evaporation and the residue is recrystallised from isopropanol. The resulting 5-(4-pyridyl)-2,3,5,6-tetrahydro-imidazo[1,2-c]quinazoline 5-acetic acid ethyl ester melts at 190 - 192°. During

the above-mentioned filtration through silica gel there is obtained, as by-product, 5-methyl-5-(4-pyridyl)-2,3,5,6-tetrahydro-imidazo[1,2-c]quinazoline having a melting point of 226 - 228° (from isopropanol).

Analogously, 5-(4-pyridyl)-2,3,5,6-tetrahydro-imidazo[1,2-c]quinazoline 5-acetic acid ethyl ester can also be obtained if, instead of 2-(2-aminophenyl)-4,5-dihydro-1H-imidazole, a corresponding salt, for example 2-(2-aminophenyl)-4,5-dihydro-1H-imidazole dihydrochloride hydrate (J. Med. Chem. *13*, 697-704 (1970)) is used in the reaction.

Example 8

18.22 g (0.1 mol) of benzophenone are added at 0° to a solution of 8.06 g (0.05 mol) of 2-(2-aminophenyl)-4,5-dihydro-1H-imidazole in 125 ml of 1.8N methanolic hydrogen chloride solution. The reaction mixture is stirred for 15 hours at room temperature. Ether is added and the resulting precipitate of the hydrochloride of 5,5-diphenyl-2,3,5,6-tetrahydro-imidazo[1,2-c]quinazoline is filtered off. The latter is recrystallised twice from ethanol/ether. It melts at above 300°.

Analogously, using 5.8 g (0.1 mol) of acetone, 5,5-dimethyl-2,3,5,6-tetrahydro-imidazo[1,2-c]quinazoline hydrochloride having a melting point of 249 - 250° (from ethanol/ether) is obtained.

Example 9

Analogously to Example 8, 8.06 g (0.05 mol) of 2-(2-aminophenyl)-4,5-dihydro-1H-imidazole and 8.10 g (0.06 mol) of methyl 2-pyridylmethyl ketone [cf. Helv. Chim. Acta *45*, 729 (1962)] are reacted in 125 ml of 1.8N methanolic hydrogen chloride solution. The reaction mixture is, however, concentrated by evaporation and the residue is recrystallised from ethanol/ether and chloroform/methanol/ether. The dihydrochloride of 5-methyl-[(2-pyridyl)-methyl]-2,3,5,6-tetrahydro-imidazo[1,2-c]quinazoline begins to decompose at approximately 150°.

Example 10

Analogously to Example 8, 8.06 g (0.05 mol) of 2-(2-aminophenyl)-4,5-dihydro-1H-imidazole and 6.75 g (0.05 mol) of methyl 6-methyl-2-pyridyl ketone [cf. J. Med. Pharm. Chem. *3*, 561 (1961)] are reacted in 125 ml of 1.8N methanolic hydrogen chloride solution. The reaction mixture is, however, concentrated by evaporation and the residue is recrystallised from water and ethanol/ether. The hydrochloride of 5-methyl-5-(6-methyl-2-pyridyl)-2,3,5,6-tetrahydro-imidazo[1,2-c]quinazoline melts at 269 - 270°.

Example 11

Analogously to Example 8, 8.06 g (0.05 mol) of 2-(2-aminophenyl)-4,5-dihydro-1H-imidazole and 10.13 g (0.055 mol) of di- (2-pyridyl) ketone [cf. Rec. trav. chim. *70*, 1054 (1951)] are reacted in 240 ml of 1.8 N methanolic hydrogen chloride solution. The reaction mixture is, however, concentrated by evaporation, the residue is dissolved in water and the solution is adjusted to pH 8 with 2N sodium hydroxide solution. The precipitate that has formed is filtered off and recrystallised from ethanol/ether. The resulting hydrochloride of 5,5-di-(2-pyridyl)-2,3,5,6-tetrahydro-imidazo[1,2-c]quinazoline melts at above 300°.

Example 12

A gently boiling, concentrated solution of 2.32 g (0.02 mol) of maleic acid is added at the boiling temperature to a likewise gently boiling, concentrated ethanolic solution of 5.28 g (0.02 mol) of 5-methyl-5-(4-pyridyl)-2,3,5,6-tetrahydro-imidazo[1,2-c]quinazoline. After cooling, the maleate that has formed is filtered off and recrystallised from isopropanol, whereupon it melts at 170 - 171°.

Analogously, using 2.32 g (0.02 mol) of fumaric acid, the corresponding fumarate is obtained. After recrystallisation from methanol, the fumarate melts at 237 - 239°.

Example 13

Analogously to Example 1, 8.06 g (0.05 mol) of 2-(2-aminophenyl)-4,5-dihydro-1H-imidazole and 12.24 g (0.075 mol) of butyl 4-pyridyl ketone [cf. J. Chem. Soc. (C) 1969, 2134] are reacted in 150 ml of 2.7N methanolic hydrogen chloride solution. In working up, instead of 1N sodium hydroxide solution, dilute aqueous ammonia solution is used. The resulting 5-butyl-5-(4-pyridyl)-2,3,5,6-tetrahydro-imidazo[1,2-c]quinazoline melts at 257 - 259° after recrystallisation from ethyl acetate.

Analogously, using 15.40 g (0.075 mol) of heptyl 4-pyridyl ketone [cf. J. Med. Chem. *14*, 551 (1971)], 5-heptyl-5-(4-pyridyl)-2,3,5,6-tetrahydro-imidazo[1,2-c]quinazoline having a melting point of 161 - 163° (from acetone/petroleum ether) is obtained and, using 15.85 g (0.075 mol) of phenethyl 4-pyridyl ketone [cf. J. Chem. Soc. (C) 1969, 2134], 5-phenethyl-5-(4-pyridyl)-2,3,5,6-tetrahydro-imidazo[1,2-c]quinazoline having a melting point of 187 - 188° (from ethyl acetate) is obtained.

Example 14

Analogously to Example 13, 6.44 g (0.04 mol) of 2-(2-aminophenyl)-4,5-dihydro-1H-imidazole and 11.0 g (0.06 mol) of phenyl 4-pyridyl ketone are reacted, the reaction mixture, however, being stirred for 40 hours at room temperature and then boiled for 2 hours under reflux. The resulting 5-phenyl-5-(4-pyridyl)-2,3,5,6-tetrahydro-imidazo-[1,2-c]quinazoline melts at 198 - 200° after recrystallisation from chloroform/ether and then from ethyl acetate.

Example 15

Analogously to Example 1, but observing a reaction period of 15 hours, starting from 3.91 g (0.02 mol) of 2-(2-amino-5-chlorophenyl)-4,5-dihydro-1H-imidazole, 4.47 g (0.03 mol) of propyl 4-pyridyl ketone and 50 ml of 2N methanolic hydrogen chloride solution, 5-propyl-5-(4-pyridyl)-9-chloro-2,3,5,6-tetrahydro-imidazo[1,2-c]quinazoline having a melting point of 181.5 - 183° after recrystallisation from chloroform/ether and then from ethyl acetate is obtained.

The 2-(2-amino-5-chlorophenyl)-4,5-dihydro-1H-imidazole is obtained as follows:

a) A solution of 15.26 g (0.1 mol) of 2-amino-5-chlorobenzonitrile, 6.0 g (0.1 mol) of 1,2-ethanediamine and 20 drops of carbon disulphide in 100 ml of ethanol is boiled under reflux for 22 hours. After adding a further 3.0 g (0.05 mol) of 1,2-ethanediamine and 20 drops of carbon disulphide, the mixture is boiled under reflux for a further 50 hours, the reaction mixture is then concentrated by evaporation *in vacuo* and the residue is recrystallised from methylene chloride/hexane. The resulting 2-(2-amino-5-chlorophenyl)-4,5-dihydro-1H-imidazole melts at 105 - 107°.

Example 16

Analogously to Example 15, starting from 8.05 g (0.05 mol) of 2-(2-aminophenyl)-4,5-dihydro-1H-imidazole, 8.15 g (0.055 mol) of phenyl propyl ketone and 150 ml of 2.5N methanolic hydrogen chloride solution, 5-phenyl-5-propyl-2,3,5,6-tetrahydro-imidazo[1,2-c]quinazoline having a melting point of 247 - 249° (from methanol/ether) is obtained.

Example 17

Analogously to Example 1, but with boiling under reflux for 22 hours, starting from 9.46 g (0.05 mol) of 2-(2-amino-4,6-dimethylphenyl)-4,5-dihydro-1H-imidazole, 11.93 g (0.08 mol) of propyl 4-pyridyl ketone and 165 ml of 2.5N methanolic hydrogen chloride solution, 5-propyl-5-(4-pyridyl)-8,10-dimethyl-2,3,5,6-tetrahydro-imidazo[1,2-c]-quinazoline having a melting point of 187 - 189° after recrystallisation from ether and from ethyl acetate/hexane is obtained. Further reaction product can be obtained if the mother liquor is concentrated by evaporation after the first recrystallisation from ether and the residue, which still contains starting materials, is boiled under reflux again with 80 ml of 2.5N methanolic hydrogen chloride solution for 15 hours.

The 2-(2-amino-4,6-dimethylphenyl)-4,5-dihydro-1H-imidazole is obtained as follows:

a) A mixture of 21.93 g (0.15 mol) of 2-amino-4,6-dimethylbenzonitrile [cf. Polish Journal of Chemistry *52*, 1389 (1978)] and 34.85 g (0.15 mol) of 2-aminoethylammonium toluene-4-sulphonate [cf. J. Chem. Soc., 497 (1947)] is heated for 3 hours, while stirring, at a bath temperature of 250°, during which ammonia is liberated from the melt. A further 20 g (0.086 mol) of 2-aminoethylammonium toluene-4-sulphonate are added and the mixture is heated for a further 3½ hours at a bath temperature of 250 - 260°. After cooling, the reaction mixture is partitioned between chloroform and 10% sodium hydroxide solution, the organic phase is washed with water, dried over sodium sulphate and concentrated by evaporation. After adding ether to the residue, the crude 2-(2-amino-4,6-dimethylphenyl)-4,5-dihydro-1H-imidazole crystallises out and, after recrystallisation from ethyl acetate, melts at 141 - 142°.

Example 18

9.46 (0.05 mol) of 2-(2-amino-4,6-dimethylphenyl)-4,5-dihydro-1H-imidazole [cf. Example 17a)] and 13.74 g (0.075 mol) of phenyl 4-pyridyl ketone are boiled under reflux in 200 ml of 2.5N methanolic hydrogen chloride solution for 22 hours. After working up analogously to Example 7, the resulting 5-phenyl-5-(4-pyridyl)-8,10-dimethyl-2,3,5,6-tetrahydro-imidazo[1,2-c]quinazoline melts at 249 - 251° (from isopropanol/ether).

Example 19

0.28 g (0.0064 mol) of sodium hydride dispersion (55% in oil) is added to a suspension of 1.32 g (0.005 mol) of 5-methyl-5-(4-pyridyl)-2,3,5,6-tetrahydro-imidazo[1,2-c]-quinazoline in 13 ml of dimethylformamide and the mixture is stirred for one hour at 70°. After cooling to room temperature, 0.91 g (0.0064 mol) of methyl iodide is added dropwise. The mixture is stirred for a further 10 minutes, it is then cooled to 0°, 2 ml of water are added dropwise to the reaction mixture, it is concentrated by evaporation *in vacuo* and the residue is partitioned between ethyl acetate and water. The organic phase is washed with water, dried over magnesium sulphate and concentrated by evaporation. After recrystallisation of the residue from ethyl acetate/petroleum ether, pure 5,6-dimethyl-5-(4-pyridyl)-2,3,5,6-tetrahydro-imidazo[1,2-c]quinazoline having a melting point of 153 - 154° is obtained.

Example 20

Analogously to Example 1, but with boiling under reflux for 7 hours, using 9.46 g (0.05 mol) of 2-(2-amino-phenyl)-4,4(or 5,5)-dimethyl-4,5-dihydro-1H-imidazole (cf. US 3894040 and US 3920687), 9.08 g (0.075 mol) of methyl 4-pyridyl ketone and 160 ml of 2.5N methanolic hydrogen chloride solution, 2,2,5-trimethyl-5-(4-pyridyl)-2,3,5,6-tetrahydro-imidazo[1,2-c]quinazoline having a melting point of 138 - 141° (from ethyl acetate/hexane) is obtained.

Example 21

15.92 g (0.1 mol) of 2-(2-aminophenyl)-1H-imidazole [cf. Il Farmaco, Ed. Sc. *30*, 536 (1975)] and 20.89 g (0.14 mol) of propyl 4-pyridyl ketone are stirred in 240 ml of 2.5N methanolic hydrogen chloride solution for 15 hours at 20° and then boiled under reflux for a further 12 hours. The reaction mixture is then evaporated to dryness and the residue is partitioned between 2N sodium hydroxide solution and chloroform. The organic phase is washed with water, dried over sodium sulphate and concentrated by evaporation. The 5-propyl-5-(4-pyridyl)-5,6-dihydro-imidazo[1,2-c]quinazoline obtained after recrystallisation of the residue from ethyl acetate melts at 199 - 200°.

Example 22

Analogously to Example 1, but observing a reaction period of 20 hours at 20°, starting from 3.18 g (0.02 mol) of 2-(2-aminophenyl)-1H-imidazole, 3.63 g (0.03 mol) of methyl 4-pyridyl ketone and 50 ml of 3N methanolic hydrogen chloride solution, 5-methyl-5-(4-pyridyl)-5,6-dihydroimidazo[1,2-c]quinazoline having a melting point of 208 - 210° (from chloroform/ether) is obtained.

Example 23

A solution of 8.76 g (0.05 mol) of 2-(2-aminophenyl)-1,4,5,6-tetrahydro-pyrimidine [cf. J. Heterocyclic Chem. *15*, 877 (1978)] and 13.74 g (0.075 mol) of phenyl 2-pyridyl ketone in 125 ml of 2.5N methanolic hydrogen chloride solution is boiled under reflux for 48 hours and then concentrated by evaporation. The residue is partitioned between 2N sodium hydroxide solution and chloroform, the organic phase is washed with water and, after drying over sodium sulphate, is concentrated by evaporation *in vacuo*. The oily residue crystallises on being stirred with ether. After recrystallisation from ethanol/hexane, the resulting 6-phenyl-6-(2-pyridyl)-3,4,6,7-tetrahydro-2H-pyrimido[1,2-c]quinazoline melts at 218 - 219°.

Analogously, there are obtained:

using 17.1 g (0.075 mol) of 3-nitrophenyl 4-pyridyl ketone [cf. Monatshefte Für Chemie *107*, 1449 (1976)], 6-(3-nitrophenyl)-6-(4-pyridyl)-3,4,6,7-tetrahydro-2H-pyrimido[1,2-c]quinazoline having a melting point of 115 - 117° (from ethyl acetate; the compound contains one mol of ethyl acetate);

using 13.81 g (0.075 mol) of 2,2'-dipyridyl ketone - but with boiling under reflux in 150 ml of 3N methanolic hydrogen chloride slution for 20 hours - 6,6-di-(2-pyridyl)-3,4,6,7-tetrahydro-2H-pyrimido[1,2-c]quinazoline having a melting point of 265 - 266° (from methanol);

using 11.12 g (0.075 mol) of phenyl propyl ketone - but while heating in a bomb tube at 150° for 4 hours - 6-phenyl-6-propyl-3,4,6,7-tetrahydro-2H-pyrimido [1,2-c]-quinazoline having a melting point of 190 - 192° (from ethyl acetate);

and, by reaction of 8.76 g (0.05 mol) of 2-(2-amino-phenyl)-1,4,5,6-tetrahydro-pyrimidine with 8.7 g (0.15 mol) of acetone in 100 ml of 2.5N methanolic hydrogen chloride solution for 15 hours at 20°, 6,6-dimethyl-3,4,6,7-tetrahydro-2H-pyrimido [1,2-c] quinazoline having a melting point of 218 - 220° (from ethyl acetate).

The starting compound, 2-(2-aminophenyl)-1,4,5,6-tetrahydro-pyrimidine can also be obtained in the following manner:

a) A mixture of 50 g (0.42 mol) of 2-aminobenzonitrile, 62.27 g (0.84 mol) of 1,3-propanediamine and 5 drops of carbon disulphide is heated at 150° for 24 hours while stirring and introducing nitrogen, ammonia being evolved. The reaction mixture is then concentrated by evaporation *in vacuo* and the residue is taken up in ether. The 2-(2-aminophenyl)-1,4,5,6-tetrahydro-pyrimidine crystallises out of the ethereal solution, m.p. 99 - 101°.

Example 24

20 g of molecular sieve (3×10^{-10}m, pearl form approximately 2 mm; Merck) are added to a solution of 34.0 g (0.194 mol) of 2-(2-aminophenyl)-1,4,5,6-tetrahydro-pyrimidine and 53.3 g (0.291 mol) of phenyl 4-pyridyl ketone in 300 ml of 3N methanolic hydrogen chloride solution and the reaction mixture is boiled under reflux for 16 hours. The molecular sieve is filtered off, the filtrate is concentrated by evaporation and the residue is worked up analogously to Example 23. The resulting 6-phenyl-6-(4-pyridyl)-3,4,6,7-tetrahydro-2H-pyrimido[1,2-c]quinazoline melts at 243 - 245° (from isopropanol/ether).

Analogously, 6-phenyl-6-(4-pyridyl)-2,4,6,7-tetrahydro-2H-pyrimido[1,2-c]quinazoline can also be obtained if, instead of 2-(2-aminophenyl)-1,4,5,6-tetrahydro-pyrimidine, a corresponding salt, for example 2-(2-aminophenyl)-1,4,5,6-tetrahydro-pyrimidine dihydrochloride (cf. J. Med. Chem. *13*, 697-704 (1970)), or, instead of the free ketone, the imine thereof, is used in the reaction.

Example 25

A solution of 13.15 g (0.075 mol) of 2-(2-aminophenyl)-1,4,5,6-tetrahydro-pyrimidine and 10.41 g (0.086 mol) of methyl 4-pyridyl ketone in 200 ml of 1.83N methanolic hydrogen chloride solution is stirred for 2½ days at 20°. The reaction mixture is subsequently concentrated to approximately half the original volume, ether is added, the precipitate that has formed is filtered off and partitioned between chloroform and 1N sodium hydroxide solution. The organic phase, washed with water, is dried over sodium sulphate and concentrated by evaporation, and the residue is recrystallised from isopropanol. The resulting 6-methyl-6-(4-pyridyl)-3,4,6,7-tetrahydro-2H-pyrimido[1,2-c]quinazoline melts at 207 - 209°.

Example 26

8.76 g (0.05 mol) of 2-(2-aminophenyl)-1,4,5,6-tetrahydro-pyrimidine and 13.74 g (0.075 mol) of phenyl 2-pyridyl ketone are stirred in 90 g of polyphosphoric acid for 3 hours at 150°. The reaction mixture is cooled, ice-water and an excess of aqueous ammonia solution are added thereto, the reaction mixture is extracted with chloroform and the organic phase is concentrated by evaporation *in vacuo* after being dried over sodium sulphate. The oily residue crystallises on being stirred with ether. The resulting 6-phenyl-6-(2-pyridyl)-3,4,6,7-tetrahydro-2H-pyrimido[1,2-c]quinazoline melts at 218 - 219° (from ethanol/hexane).

Analogously, starting from 13.74 g (0.075 mol) of phenyl 4-pyridyl ketone - but with a reaction period of 2 hours at 130° and 4 hours at 150° and using 140 g of polyphosphoric acid - 6-phenyl-6-(4-pyridyl)-3,4,6,7-tetrahydro-2H-pyrimido[1,2-c]quinazoline having a melting point of 243 - 246° (from isopropanol/ether) is obtained.

Example 27

A solution of 8.76 g (0.05 mol) of 2-(2-aminophenyl)-1,4,5,6-tetrahydro-pyrimidine and 11.18 g (0.075 mol) of propyl 4-pyridyl ketone in 200 ml of 2N methanolic hydrogen chloride solution is boiled under reflux for 2 days and worked up analogously to Example 23. The resulting 6-propyl-6-(4-pyridyl)-3,4,6,7-tetrahydro-2H-pyrimido[1,2-c]-quinazoline melts at 221 - 223° (from ethanol/ether).

The mother liquor obtained in recrystallisation, which still contains starting materials, is concentrated by evaporation and the residue is stirred with 60 g of polyphosphoric acid for one hour at 120°. The reaction mixture is cooled, ice-water and an excess of aqeuous ammonia solution are added, the reaction mixture is extracted with chloroform and the organic phase is concentrated by evaporation after being dried over sodium sulphate. The residue is recrystallised from ethanol/ether. In this manner, a second batch of 6-propyl-6-(4-pyridyl)-3,4,6,7-tetrahydro-2H-pyrimido[1,2-c]quinazoline having a melting point of 221 - 223° is obtained.

Analogously, using 12.24 g (0.075 mol) of butyl 4-pyridyl ketone, 6-butyl-6-(4-pyridyl)-3,4,6,7-tetrahydro-2H-

Example 28

A mixture of 17.52 g (0.1 mol) of 2-(2-aminophenyl)-1,4,5,6-tetrahydro-pyrimidine, 27.48 g (0.15 mol) of phenyl 4-pyridyl ketone and 0.3 g of toluene 4-sulphonic acid monohydrate is stirred for 24 hours at 180° and under a pressure of approximately 270 mbar. After cooling, the melt is taken up in ethyl acetate. In so doing, crude 6-phenyl-6-(4-pyridyl)-3,4,6,7-tetrahydro-2H-pyrimido[1,2-c]quinazoline precipitates which, after re-crystallisation from isopropanol/ether, melts at 243 - 245°.

Example 29

While stirring and introducing nitrogen, a mixture of 20 g (0.114 mol) of 2-(2-aminophenyl)-1,4,5,6-tetrahydropyrimidine and 31.2 g (0.170 mol) of phenyl 4-pyridyl ketone is introduced at 160° into a melt consisting of 100 g of anhydrous aluminium chloride and 50 g of sodium chloride, the temperature temporarily rising to 205°. When the addition is complete, the reaction mixture is stirred for a further 20 minutes at 180° and the melt is then allowed to solidify while cooling. The reaction material is dissolved in 700 ml of hot water. Washing with chloroform is carried out and 500 ml of concentrated aqueous ammonia solution are added to the aqueous phase. The alkaline phase is stirred thoroughly with 500 ml of chloroform for 3 hours and, after the addition of 300 g of kieselguhr, the mixture is filtered. The chloroform phase of the filtrate is dried over sodium sulphate and concentrated by evaporation *in vacuo*. After recrystallisation of the residue from ethyl acetate and from isopropanol/ether, the resulting 6-phenyl-6-(4-pyridyl)-3,4,6,7-tetrahydro-2H-pyrimido[1,2-c]quinazoline melts at 243 - 245°.

Example 30

1.92 g (0.02 mol) of methanesulphonic acid is added to a solution of 6.8 g (0.02 mol) of 6-phenyl-6-(4-pyridyl)-3,4,6,7-tetrahydro-2H-pyrimido[1,2-c]quinazoline in methanol. The mixture is concentrated by evaporation and the residue is recrystallised from ethanol/ethyl acetate. The resulting 6-phenyl-6-(4-pyridyl)-3,4,6,7-tetrahydro-2H-pyrimido[1,2-c]-quinazoline methanesulphonate melts at 249 - 250°.

Upon recrystallising the above methanesulphonate from ethanol with a little water, adding hexane until the mixture becomes opaque, filtering and drying, depending on the method of drying the methanesulphonate monohydrate or the methanesulphonate dihydrate is obtained both of which melt at 248 - 251° (with sintering from 100°).

Example 31

Analogously to Example 23, starting from 8.76 g (0.05 mol) of 2-(2-aminophenyl-1,4,5,6-tetrahydro-pyrimidine and 13.74 g (0.075 mol) of phenyl 3-pyridyl ketone, crude 6-phenyl-6-(3-pyridyl)-3,4,6,7-tetrahydro-2H-pyrimido[1,2-c]-quinazoline is obtained which is filtered over silica gel having a particle size of 0.063 - 0.200 mm with a mixture of chloroform:methanol:concentrated ammonia = 40:10:1. The fractions containing the desired product are concentrated by evaporation and the oily residue is dissolved in methanol. To this solution is added a methanolic solution of an equi-molar amount of fumaric acid. After

concentration by evaporation *in vacuo*, the residue is recrystallised from methanol/ethyl acetate. The resulting 6-phenyl-6-(3-pyridyl)-3,4,6,7-tetrahydro-2H-pyrimido[1,2-c]quinazoline fumarate contains 1.5 mol of fumaric acid and melts at 223 - 225°.

Example 32

Analogously to Example 25, starting from 17.52 g (0.1 mol) of 2-(2-aminophenyl)-1,4,5,6-tetrahydro-pyrimidine, 29.55 g (0.15 mol) of 4-methylphenyl 4-pyridyl ketone [cf. Helv. Chim. Acta *52* 262 (1969)], 150 ml of 2.5N methanolic hydrogen chloride solution and 15 g of molecular sieve (3 × 10^{-10}m, pearl form approximately 2 mm; Merck), crude 6-(4-methylphenyl)-6-(4-pyridyl)-3,4,6,7-tetrahydro-2H-pyrimido[1,2-c]quinazoline is obtained which is chromatographed over silica gel having a particle size of 0.063 - 0.200 mm with a mixture of chloroform:methanol:concentrated ammonia = 40:10:1 as solvents and eluants. The uniform fractions containing the desired product are concentrated by evaporation. The residue is dissolved in ethanol and an equivalent amount of methanesulphonic acid is added to the ethanolic solution. After renewed concentration by evaporation and recrystallisation of the residue from ethanol/hexane, the resulting 6-(4-methylphenyl)-6-(4-pyridyl)-3,4,6,7-tetrahydro-2H-pyrimido[1,2-c]quinazoline methane-sulphonate melts at 257 - 259°.

Example 33

A mixture of 17.52 g (0.1 mol) of 2-(2-aminophenyl)-1,4,5,6-tetrahydro-pyrimidine, 18.32 g (0.1 mol) of phenyl 4-pyridyl ketone, 500 ml of toluene and 70 g of silica gel having a particle size of 0.063 - 0.200 mm is boiled in a water separator, while stirring, for 18 hours, then a further 20 g of silica gel are added and the mixture is boiled for a further 15 hours in the water separator. After filtration and washing of the filter material with a chloroform/methanol mixture (1:1), the filtrate is concentrated by evaporation *in vacuo* and ethyl acetate is added to the residue, whereupon 6-phenyl-6-(4-pyridyl)-3,4,6,7-tetrahydro-2H-pyrimido[1,2-c]quinazoline precipitates which melts at 234 - 237°.

Example 34

Analogously to Example 19, 12.75 g (0.0375 mol) of 6-phenyl-6-(4-pyridyl)-3,4,6,7-tetrahydro-2H-pyrimido[1,2-c]-quinazoline, 2.19 g (0.05 mol) of sodium hydride dispersion (55% in oil) and 7.8 g (0.05 mol) of ethyl iodide are reacted in 110 ml of dimethylformamide. Stirring is, however, carried out for 12 hours at room temperature, 10 ml of water are then added dropwise to the reaction mixture, while cooling, the reaction mixture is concentrated by evaporation *in vacuo* and the residue is partitioned between chloroform and 1N sodium hydroxide solution. The organic phase is washed with water, dried over sodium sulphate and concentrated by evaporation. The residue is chromatographed over silica gel having a particle size of 0.063 - 0.200 mm with a mixture of chloroform:methanol:concentrated ammonia = 14:6:1 as solvents and eluants. The uniform fractions containing the desired product are concentrated by evaporation and the residue is recrystallised from ethanol/hexane. The resulting 6-phenyl-6-(4-pyridyl)-7-ethyl-3,4,6,7-tetrahydro-2H-pyrimido[1,2-c]quinazoline melts at 230 - 231°. The fumarate manufactured therefrom with fumaric acid melts at 252 - 254° (from ethanol/methanol 10:1).

Example 35

Analogously to Example 1, but with boiling under reflux for 5 hours, starting from 11.16 g (0.059 mol) of 2-(2-aminophenyl)-4,4(or 5,5)-dimethyl-4,5-dihydro-1H-imidazole, 13.27 g (0.089 mol) of propyl 4-pyridyl ketone and 150 ml of 3N methanolic hydrogen chloride solution, 2,2-dimethyl-5-propyl-5-(4-pyridyl)-2,3,5,6-tetrahydroimidazo[1,2-c]quinazoline having a melting point of 224 - 226° after recrystallisation from ethyl acetate and then from ethanol/ether is obtained.

Example 36

Analogously to Example 33, using 16.32 g (0.1 mol) of 2-(2-aminophenyl)-4,5-dihydro-1H-imidazole and 21.83 g (0.1 mol) of 4-methoxyphenyl 2-thienyl ketone, but with boiling under reflux for 7 days and chromatography of the crude product over silica gel having a particle size of 0.063 - 0.200 mm with a mixture of chloroform:methanol = 9:1, 5-(4-methoxyphenyl)-5-(2-thienyl)-2,3,5,6-tetrahydro-imidazo-[1,2-c]quinazoline having a melting point of 207 - 208° (from acetone and ethyl acetate) is obtained.

Example 37

11.68 g (0.05 mol) of 2-chloro-5-acetyl-benzenesulphonamide [Arzneimittelforsch. *13*, 269-280 (1963)] are added to a solution of 8.06 g (0.05 mol) of 2-(2-aminophenyl)-4,5-dihydro-1H-imidazole in 140 ml of 2.6N methanolic hydrogen chloride solution and the reaction mixture is stirred for 72 hours at 20°. The precipitate that has formed is filtered off and suspended in 360 ml of water, and the suspension is stirred for ½ hour at room temperature with an excess of 30% aqueous ammonia solution. After filtration and recrystallisation of the residue from methanol, the resulting 5-(4-chloro-3-sulphamoyl-phenyl)-5-methyl-2,3,5,6-tetrahydro-imidazo[1,2-c]quinazoline melts at 274° (with decomposition).

Example 38

17.52 g (0.1 mol) of 2-(2-aminophenyl)-1,4,5,6-tetrahydro-pyrimidine, 21.32 g (0.1 mol) of 4-methoxyphenyl 4-pyridyl ketone (J. Pharm. Sci. *62*, 847-9 (1973)) and 43.2 g (0.1 mol) of polyphosphate ester (PPE, Fieser & Fieser, Reagents for Organic Synthesis, New York 1967, page 892) are boiled under reflux in 250 ml of chloroform for 96 hours. The reaction mixture is subsequently stirred with an excess of 2N sodium hydroxide solution. The organic phase is then separated, washed with a little water, dried over sodium sulphate and concentrated by evaporation. Ethylene chloride is added to the residue, whereupon the desired 6-(4-methoxyphenyl)-6-(4-pyridyl)-3,4,6,7-tetrahydro-2H-pyrimido[1,2-c]-quinazoline precipitates. It melts at 236 - 238° (from ethylene chloride).

Example 39

17.52 g (0.1 mol) of 2-(2-aminophenyl)-1,4,5,6-tetrahydro-pyrimidine, 18.32 g (0.1 mol) of phenyl 4-pyridyl ketone and 43.2 g (0.1 mol) of polyphosphate ester are boiled under reflux for 45 hours in 150 ml of chloroform while stirring and gently introducing nitrogen. After cooling the reaction mixture and adding 250 ml of 2N sodium hydroxide solution and 200 ml of chloroform, the reaction mixture is stirred for a further 15 minutes at room temperature, the chloroform phase is subsequently separated and the aqueous phase is extracted another two times with 150 ml of chloroform each time. The combined organic phases, washed with a little water and dried over sodium sulphate, are concentrated by evaporation and the oily residue is stirred with 100 ml of ethyl acetate, whereupon the desired 6-phenyl-6-(4-pyridyl)-3,4,6,7-tetrahydro-2H-pyrimido[1,2-c]-quinazoline precipitates which, after washing with ethyl acetate and ether, melts at 237 - 239°. After an additional recrystallisation from ethanol/hexane, the product melts at 240 - 242°.

Example 40

17.52 g (0.1 mol) of 2-(2-aminophenyl)-1,4,5,6-tetrahydro-pyrimidine, 23.93 g (0.1 mol) of 4-(1,1,-dimethyl-ethyl)-phenyl 4-pyridyl ketone [J. Pharm. Sci. *62*, 847-849 (1973)] and 43.2 g (0.1 mol) of polyphosphate ester are boiled under reflux in 250 ml of chloroform for 24 hours. The reaction mixture is cooled and, while stirring vigorously, 260 ml of semi-concentrated (approx. 12.5 % in water) ammonia solution are added. After stirring for 15 minutes, the chloroform phase is separated off, dried over sodium sulphate and concentrated by evaporation. The residue is filtered over silica gel having a particle size of 0.063 - 0.200 mm with a mixture of chloroform:methanol:concentrated ammonia = 40:10:1 and the fractions containing the desired product are concentrated by evaporation. After recrystallisation from acetonitrile and methylene chloride/hexane the resulting 6-[4-(1-1-dimethylethyl)-phenyl]-6-[4-pyridyl]-3,4,6,7-tetrahydro-2H-pyrimido[1,2-c]quinazoline melts at 142 - 145°.

Example 41

600 ml of xylene are added to 70 g of silica gel H according to Stahl (for example of E. Merck AG, Darmstadt) and the mixture is heated, while stirring, in a water separator until no more water separates. The mixture is cooled, 17.52 g (0.1 mol) of 2-(2-aminophenyl)-1,4,5,6-tetrahydro-pyrimidine and 18.32 g (0.1 mol) of phenyl 4-pyridyl ketone are added and the reaction mixture is boiled in a water separator for 95 hours. After filtration and washing of the filtration residue with ether, the filter material is continuously extracted with chloroform. The extract is concentrated by evaporation and ethyl acetate is added to the resulting residue, whereupon 6-phenyl-6-(4-pyridyl)-3,4,6,7-tetrahydro-2H-pyrimido[1,2-c]quinazoline precipitates which melts at 241 - 243°.

Example 42

Analogously to Example 41, but using toluene as solvent and heating the reaction mixture for 40 hours, starting from 17.52 g (0.1 mol) of 2-(2-aminophenyl)- 1,4,5,6-tetrahydro-pyrimidine and 21.77 g (0.1 mol) of 4-chlorophenyl 4-pyridyl ketone, 6-(4-chlorophenyl)-6-(4-pyridyl)-3,4,6,7-tetrahydro-2H-pyrimido[1,2-c]quinazoline is obtained which, after recrystallisation from ethylene chloride and acetonitrile, melts at 215 - 217°.

Example 43

Analogously to Example 41, but using toluene and heating for 72 hours, 8.76 g (0.05 mol) of 2-(2-aminophenyl)-1,4,5,6-tetrahydro-pyrimidine and 9.46 g (0.05 mol) of 4-pyridyl 2-thienyl ketone (J. Med. Chem. *12*, 1093-6 (1969)) are reacted. After filtration and washing of the filter material with a solvent mixture of chloroform: methanol = 1:1, the filtrate is concentrated by evaporation. Ethyl acetate is added to the residue, whereupon crude 6-(4-pyridyl)-6-(2-thienyl)-3,4,6,7-tetrahydro-2H-pyrimido-[1,2-c]quinazoline precipitates which, after recrystallisation from ethanol/hexane, melts at 208 - 210°.

Example 44

Analogously to Example 41, 17.52 g (0.1 mol) of 2-(2-aminophenyl)-1,4,5,6-tetrahydro-pyrimidine and 19.92 g (0.1 mol) of 4-hydroxyphenyl 4-pyridyl ketone are reacted using 500 ml of chlorobenzene as solvent. After filtration and washing of the silica gel with ether, the filter material is stirred three times, while heating, with 300 ml of a mixture of chloroform:methanol = 1:1 each time and then filtered. The combined filtrates are concentrated by evaporation and the residue is purified by chromatography over silica gel with a mixture

of chloroform:methanol:concentrated ammonia = 40:10:1. The fractions containing the desired product are combined and concentrated by evaporation. The crystalline residue is boiled in methanol, cooled and filtered. The resulting 6-(4-hydroxyphenyl)-6-(4-pyridyl)-3,4,6,7-tetrahydro-2H-pyrimido[1,2-c]quinazoline hemihydrate melts at 287 - 289° (with decomposition).

The starting compound, 4-hydroxyphenyl 4-pyridyl ketone, is manufactured as follows:

A solution of 187.9 g (0.75 mol) of boron tribromide in 750 ml of methylene choride is added dropwise at 5°, while stirring, to a solution of 53.3 g (0.25 mol) of 4-methoxyphenyl 4-pyridyl ketone in 500 ml of methylene chloride. The reaction mixture is stirred at room temperature for 15 hours and subsequently extracted with an excess of 2N sodium hydroxide solution. The alkaline phase is washed with chloroform and is subsequently rendered acidic (pH approx. 5) with glacial acetic acid. The precipitate that has formed is filtered off and the filter material is washed with isopropanol. After recrystallisation from dimethylformamide/water, the resulting 4-hydroxyphenyl 4-pyridyl ketone melts at 257 - 259°. (cf. Heterocycles *2*, 423-426 (1974)).

Example 45

Analogously to Example 19, 12.75 g (0.0375 mol) of 6-phenyl-6-(4-pyridyl)-3,4,6,7-tetrahydro-2H-pyrimido[1,2-c]-quinazoline, 2.19 g (0.05 mol) of sodium hydride dispersion (55% in oil) and 7.1 g (0.05 mol) of methyl iodide are reacted in 110 ml of dimethylformamide. Stirring is, however, carried out for 12 hours at room temperature, 10 ml of water are then added dropwise to the reaction mixture, while cooling, the reaction mixture is concentrated by evaporation *in vacuo* and the residue is partitioned between chloroform and 15% sodium hydroxide solution. The organic phase, washed with water and dried over sodium sulphate, is concentrated by evaporation and the residue is chromatographed over silica gel with a mixture of chloroform:methanol:concentrated ammonia = 40:10:1. The fractions containing the desired product are concentrated by evaporation and the residue is recrystallised from chloroform/ether. The resulting 6-phenyl-6-(4-pyridyl)-7-methyl-3,4,6,7-tetrahydro-2H-pyrimido[1,2-c]quinazoline melts at 183 - 184°.

Example 46

Analogously to Example 12, using equivalent amounts of 5-propyl-5-(4-pyridyl)-2,3,5,6-tetrahydro-imidazo[1,2-c]-quinazoline and ethanolic hydrogen chloride solution, the corresponding hydrochloride is obtained which, after recrystallisation from ethanol/ether, melts at 278 - 280°.

Analogously, when an equivalent amount of fumaric acid is used, 5-propyl-5-(4-pyridyl)-2,3,5,6-tetrahydro-imidazol-[1,2-c]quinazoline fumarate having a melting point of 215 - 217° (with decomposition) is obtained.

Example 47

34.04 g (0.1 mol) of 6-phenyl-6-(4-pyridyl)-3,4,6,7-tetrahydro-2H-pyrimido[1,2-c]quinazoline is dissolved, while heating, in 300 ml of ethanol and then, while cooling, a solution of 10.22 g of 96 % sulphuric acid (0.1 mol) in 19.5 g of water is added. The sulphate which precipitates on cooling melts, after recrystallisation from ethanol/methanol = 1:3 and drying at 150° in a high vacuum, at 321 - 322° (with decomposition).

Recrystallisation of the above sulphate from water yields, after drying at 160° in a high vacuum, a sulphate (crystal modification) that melts at 278 - 280°. This can be re-converted by renewed recrystallisation from methanol/ether into the sulphate that melts at 321 - 322°.

Example 48

a) 3.33 ml of 15N sulphuric acid (0.025 mol) are added to a gently boiling solution of 17.02 g (0.05 mol) of 6-phenyl-6-(4-pyridyl)-3,4,6,7-tetrahydro-2H-pyrimido[1,2-c]quinazoline in 150 ml of ethanol. After the addition of active carbon and subsequent filtration, 100 ml of ether are added dropwise, while stirring, to the filtrate. The mixture is allowed to cool slowly to approximately 5°, and the precipitated salt is filtered off and washed with a mixture of ethanol: ether = 1:1. After drying over sodium hydroxide in a high vacuum at 160°, the resulting bis-[6-phenyl-6-(4-pyridyl)-3,4,6,7-tetrahydro-2H-pyrimido[1,2-c]quinazoline] sulphate monohydrate melts at 300 - 303°.

b) A solution of 2.55 g of 96% sulphuric acid (0.025 mol) in 10 ml of water is added, while stirring, to a suspension of 17.02 g (0.05 mol) of 6-phenyl-6-(4-pyridyl)-3,4,6,7-tetrahydro-2H-pyrimido[1,2-c]quinazoline in 30 ml of water. The resulting solution having a temperature of approximately 40° is filtered. The filtrate is allowed to cool slowly to 0° in the course of 4 hours and the product that has precipitated is filtered off. The mother liquor is concentrated *in vacuo* and, after cooling and filtration, a further batch of product is obtained. After drying the combined batches at room temperature, the bis-[6-phenyl-6-(4-pyridyl)-3,4,6,7-tetrahydro-2H-pyrimido[1,2-c]quinazoline]-sulphate has a water content of 11.63 % and melts at 235 - 240°. (Samples having a water content of 8.7% and 7.6% likewise melt at 235 - 240°).

Example 49

1.7 g (0.005 mol) of 6-phenyl-6-(4-pyridyl)-3,4,6,7-tetrahydro-2H-pyrimido[1,2-c]quinazoline and 0.79 g (0.005 mol) of benzensulphonic acid are heated to 100° in 280 ml of water. The mixture is then filtered and the filtrate is allowed to cool to 5°. The product that precipitates during cooling is filtered off, washed with water and dried. The resulting benzenesulphonate monohydrate decomposes at 164 - 166°.

Example 50

A solution of 3.05 g (0.025 mol) of benzoic acid in 10 ml of ethanol is added to a boiling solution of 8.51 g (0.025 mol) of 6-phenyl-6-(4-pyridyl)-3,4,6,7-tetrahydro-2H-pyrimido[1,2-c]quinazoline in 70 ml of ethanol. After the addition of 120 ml of ether and cooling to 5° the precipitated product is filtered off, washed with a mixture of ethanol:ether = 2:3 and then dried. The resulting benzoate melts at 241 - 243°.

Example 51

3.40 g (0.01 mol) of 6-phenyl-6-(4-pyridyl)-3,4,6,7-tetrahydro-2H-pyrimido[1,2-c]quinazoline are heated in a solution of 0.72 g (0.012 mol) of acetic acid in 5 ml of water. After cooling the solution in an ice bath, the precipitated product is filtered off, washed with a little ice-cold water and dried. The resulting acetate dihydrate melts at approximately 132-137° (with sintering from 120°).

Example 52

Analogously to Example 12, using 3.40 g (0.01 mol) of 6-phenyl-6-(4-pyridyl)-3,4,6,7-tetrahydro-2H-pyrimido[1,2-c]quinazoline and 1.16 g (0.01 mol) of fumaric acid, the corresponding fumarate is obtained which, after recrystallisation from methanol, decomposes at approximately 230°. This salt still contains 2.9 % of water.

Upon recrystallisation from water, 6-phenyl-6-(4-pyridyl)-3,4,6,7-tetrahydro-2H-pyrimido[1,2-c]quinazoline-1½-fumarate is obtained which decomposes at 232 - 235°.

Example 53

A mixture of 9.1 g (0.056 mol) of 2-amino-3-(4,5-dihydro-1H-imidazol-2-yl)-pyridine, 12.5 g (0.084 mol) of propyl 4-pyridyl ketone and 70 g of polyphosphoric acid is stirred at 150° for 18 hours. After working up analogously to Example 26, the resulting crude product is purified by filtration over silica gel with a solvent mixture of chloroform:methanol = 9:1. The fractions containing the desired product are concentrated by evaporation and the residue is recrystallised from ethyl acetate. The resulting 5-propyl-5-(4-pyridyl)-2,3,5,6-tetrahydro-imidazo[1,2-c]pyrido[3,2-e]pyrimidine melts at 182 - 183.5°.

Analogously,using 9.16 g (0.05 mol) of phenyl 4-pyridyl ketone, but with a reaction period of 24 hours at 140°C and subsequently 24 hours at 180°C, 5-phenyl-5-(4-pyridyl)-2,3,5,6-tetrahydro-imidazo[1,2-c]pyrido[3,2-e]-pyrimidine is obtained which, after recrystallisation from ethyl acetate/hexane, melts at 240 - 241°. The hydrochloride, prepared with hydrochloric acid in water, melts at 313 - 314° (water content 1.2%).

The 2-amino-3-(4,5-dihydro-1H-imidazol-2-yl)-pyridine used as starting material is manufactured as follows:

A mixture of 23.8 g (0.2 mol) of 2-amino-3-pyridine-carbonitrile [J.Heterocyclic Chem. *15*, 877-880 (1975)], 24 g (0.4 mol) of ethylenediamine and 6 drops of carbon disulphide is stirred for 2 hours at 150° and then concentrated by evaporation *in vacuo*. The crystalline residue is taken up in 200 ml of ice-cold ether. After filtration of the ether solution, the crude product obtained therefrom is recrystallised from hexane and ethanol/ether. The resulting 2-amino-3-(4,5-dihydro-1H-imidazol-2-yl)-pyridine melts at 155 - 157°.

Example 54

A mixture of 14.08 g (0.08 mol) of 4-amino-3-(1,4,5,6-tetrahydro-2-pyrimidinyl)-pyridine, 17.53 g (0.096 mol) of phenyl 4-pyridyl ketone and 240 g of polyphosphoric acid is heated, while stirring, for 43 hours at 170°, 17 hours at 180° and 24 hours at 200°. The reaction mixture is cooled, ice-water and an excess of 30% sodium hydroxide solution are added thereto, the reaction mixture is extracted with chloroform and the organic phase is concentrated by evaporation *in vacuo* after being dried over sodium sulphate. For purification, the residue is chromatographed over silica gel with a solvent mixture of chloroform:methanol: concentrated ammonia = 40:10:1. The fractions containing the desired product are concentrated by evaporation and the residue is recrystallised from ethanol/ethyl acetate/ether. The resulting 6-phenyl-6-(4-pyridyl)-3,4,6,7-tetrahydro-2H-pyrido[3,4-e]pyrimido[1,2-c]pyrimidine melts at 199 - 201° (water content: 3%).

The starting compound, 4-amino-3-(1,4,5,6-tetrahydro-2-pyrimidinyl)-pyridine, is manufactured as follows:

A mixture of 35.7 g (0.3 mol) of 4-amino-3-pyridine-carbonitrile (US-PS 3 517 021), 44.5 g (95 mol) of propylene-diamine and approximately 10 drops of carbon disulphide is stirred for 20 hours at 140°. After concentration of the reaction mixture by evaporation *in vacuo*, the residue is recrystallised from ethanol. The resulting 4-amino-3-(1,4,5,6-tetrahydro-2-pyrimidinyl)-pyridine melts at 208 - 210°.

Example 55

A mixture of 8.1 g (0.05 mol) of 4-amino-3-(4,5-dihydro-1H-imidazol-2-yl)-pyridine, 11.2 g (0.075 mol) of propyl 4-pyridyl ketone and 150 g of polyphosphoric acid is stirred for 30 hours at 150°, a further 5.6 g of propyl 4-pyridyl ketone are added and the mixture is stirred for a further 16 hours at 150°. After working up analogously to Example 26, the desired 5-propyl-5-(4-pyridyl)-2,3,5,6-tetrahydro-imidazo[1,2-c]pyrido[3,4-e]pyrimidine is obtained which, after recrystallisation from ethyl acetate, melts at 238 - 240°.

The starting compound, 4-amino-3-(4,5-dihydro-1H-imidazol-2-yl)-pyridine, is obtained as follows:

A mixture of 23.8 g (0.2 mol) of 4-amino-3-pyridine-carbonitrile, 24 g (0.4 mol) of ethylenediamine and

approximately 8 drops of carbon disulphide is stirred for 1.5 hours at 120°. A further 15 ml of ethylenediamine are added to the reaction mixture, it is heated for a further 2 hours at 120 and then concentrated by evaporation *in vacuo*. After recrystallisation from ethanol, the resulting 4-amino-3-(4,5-dihydro-1H-imidazol-2-yl)-pyrimidine melts at 198 - 199°.

Example 56

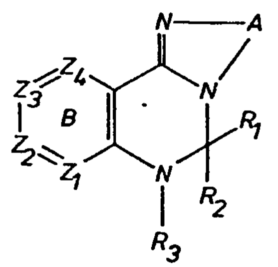
8.75 g (0.05 mol) of 2-(2-aminophenyl)-1,4,5,6-tetrahydro-pyrimidine and 10.4 g (0.05 mol) of phenyl styryl ketone (2-benzylideneacetophenone) are added to a solution of 21.7 g of polyphosphate ester in 75 ml of chloroform and the reaction mixture is boiled under reflux for 16 hours. The oily residue obtained after working up analogously to Example 39 is chromatographed over silica gel with a solvent mixture of chloroform:methanol:concentrated aqueous ammonia solution = 70:30:5. The fractions containing the desired product are concentrated by evaporation and the residue is recrystallised from acetonitrile. The 6-phenyl-6-styryl-3,4,6,7-tetrahydro-2H-pyrimido[1,2-c]quinazoline so obtained melts at 143 - 145° after drying in a high vacuum at 100°.

Example 57

50 ml of 1-n hydrochloric acid are added while stirring to a suspension of 17.02 (0.05 mol) of 6-phenyl-6-(4-pyridyl)-3,4,6,7-tetrahydro-2H-pyrimido[1,2-c]quinazoline in 100 ml of water. The suspension is brought to the boil and water is added until a solution is formed. The latter is filtered after addition of charcoal, and the filtrate is concentrated until crystallisation begins. After cooling to 5°, the salt is filtered off and washed with a small amount of ice-cold water. The 6-phenyl-6-(4-pyridyl)-3,4,6,7-tetrahydro-2H-pyrimido[1,2-c]quinazoline hydrochloride dihydrate so obtained decomposes at 345 to 347°.

CLAIMS

1. Polyazaheterocyclic compounds of the general formula I



(I)

in which

R_1 and R_2 represent, independently of each other, optionally substituted, lower aliphatic hydrocarbon radicals, optionally substituted aryl or heteroaryl each having not more than 2 rings and each being bonded directly or by way of lower alkylene or lower alkenylene,

R_3 represents hydrogen or lower alkyl,

and

A represents optionally branched lower alkylene or lower alkenylene having 2 to 4 carbon atoms in a direct chain between the adjacent nitrogen atoms,

and

Z_1, Z_2, Z_3 and Z_4 are members of the unsubstituted or substituted ring B and represent radicals –CH=, carrying the substituents of ring B, if such are present, one of which members can however also be the radical –N=, wherein R_1 and R_2 do not both represent methyl or both represent ethyl if R_3 represents hydrogen and A represents ethenylene and, at the same time, the ring B is unsubstituted, and their acid addition salts.

2. Compounds of the general formula I given in claim 1 in which R_1 and R_2 represent radicals corresponding to the definition given in claim 1 which are unsubstituted or, as lower aliphatic hydrocarbon radicals, are mono- or poly-substituted by lower alkoxy, lower alkylthio or lower alkoxycarbonyl and, as or in aryl or heteroaryl radicals each having not more than 2 rings, are mono- or poly-substituted by lower alkyl, lower alkoxy, lower alkylthio, halogen having an atomic number of not more than 35, trifluoromethyl, methylenedioxy, hydroxy, sulphamoyl, nitro or by amino optionally mono- or di-substituted by lower alkyl or amino substituted by lower alkylene or 3-oxa-1,5-lower alkylene, and together and including the optionally present substituents have from 3 to 20 carbon atoms, R_3 represents hydrogen or lower alkyl having not more than 4 carbon atoms and A represents unsubstituted ethylene, trimethylene, ethenylene, propenylene or tetramethylene, or ethylene, trimethylene, ethenylene, propenylene or tetramethylene substituted by lower alkyl, wherein substituted ethylene and trimethylene have a total of not more than 4 and 5 carbon atoms, respectively, the radicals Z_1, Z_2, Z_3 and Z_4 have the meanings given under formula I, and the ring B is unsubstituted or can be substituted in the manner stated above for aryl R_1 and R_2, and the acid addition salts thereof.

3. Compounds of the general formula I given in claim 1 in which R_1 represents monoheterocyclic monocyclic heteroaryl which is unsubstituted or substituted by lower alkyl, lower alkoxy and/or halogen having an atomic number of up to 35 and is bonded by way of methylene or directly, R_2 represents just such a radical or represents unsubstituted phenyl or phenyl substituted as stated above for monocyclic heteroaryl R_1, or unsubstituted lower alkyl or lower alkyl substituted as stated in claim 2, R_3 represents hydrogen or alkyl having not more than 4 carbon atoms, and A represents ethylene or trimethylene, the radicals Z_1, Z_2, Z_3 and Z_4 have the meanings given in claim 1 and the ring B is unsubstituted or substituted in the manner stated above for R_1, and the acid addition salts thereof.

4. Compounds of the general formula I given in claim 1, in which R_1 represents unsubstituted pyridyl or pyridyl substituted by lower alkyl, lower alkoxy and/or halogen having an atomic number of up to 35, which is bonded directly or by way of methylene, or represents unsubstituted or correspondingly substituted thienyl or furyl, R_2 represents just such a radical or unsubstituted phenyl or phenyl substituted as stated above for pyridyl R_1, or lower alkyl or lower alkoxycarbonyl-lower alkyl, R_3 represents hydrogen or alkyl having not more than 4 carbon atoms, and A represents ethylene or trimethylene, the radicals Z_1, Z_2, Z_3 and Z_4 have the meanings given in claim 1 and the ring B is unsubstituted or substituted in the manner stated above for R_1, and the acid addition salts thereof.

5. Compounds of the general formula I given in claim 1 in which R_1 represents unsubstituted pyridyl or pyridyl substituted by lower alkyl, or thienyl, R_2 represents just such a radical or unsubstituted phenyl or phenyl substituted by lower alkyl, lower alkoxy or halogen having an atomic number of up to 35, or lower alkyl or lower alkoxycarbonyl-lower alkyl, R_3 represents hydrogen or lower alkyl, A represents ethylene or trimethylene and Z_1, Z_2, Z_3 and Z_4 represent radicals $-CH=$, of which Z_2 can be substituted by halogen having an atomic number of up to 35, especially chlorine and, hence, the ring B is unsubstituted or correspondingly substituted, and the pharmaceutically acceptable acid addition salts thereof.

6. Compounds of the general formula I given in claim 1 in which R_1 represents unsubstituted pyridyl or pyridyl substituted by methyl, or 2-thienyl, R_2 represents just such a radical or unsubstituted phenyl or phenyl substituted by lower alkyl, lower alkoxy or halogen having an atomic number of up to 35, or lower alkyl or lower alkoxycarbonylmethyl, R_3 represents hydrogen, methyl or ethyl, A represents ethylene or trimethylene, and Z_1, Z_2, Z_3 and Z_4 radicals represent $-CH=$, of which Z_2 can be substituted by chlorine and, hence, the ring B is unsubstituted or correspondingly substituted, and the pharmaceutically acceptable acid addition salts thereof.

7. Compounds according to any one of claims 3 to 6 in which A is ethylene, and their pharmaceutically acceptable acid addition salts.

8. Compounds according to any one of claims 3 to 6 in which A is trimethylene, and their pharmaceutically acceptable acid addition salts.

9. 5-methyl-5-(4-pyridyl)-2,3,5,6-tetrahydro-imidazo[1,2-c]-quinazoline and its pharmaceutically acceptable acid addition salts.

10. 5-methyl-5-(6-methyl-2-pyridyl)-2,3,5,6-tetrahydro-imidazo[1,2-c]quinazoline and its pharmaceutically acceptable acid addition salts.

11. 5-butyl-5-(4-pyridyl)-2,3,5,6-tetrahydro-imidazo[1,2-c]-quinazoline and 5-propyl-5-(4-pyridyl)-2,3,5,6-tetrahydro-imidazo[1,2-c]quinazoline and their pharmaceutically acceptable acid addition salts.

12. 5-methyl-5-(2-pyridyl)-8-chloro-2,3,5,6-tetrahydro-imidazo[1,2-c]quinazoline and its pharmaceutically acceptable acid addition salts.

13. 5-phenyl-5-(4-pyridyl)-2,3,5,6-tetrahydro-imidazo[1,2-c]quinazoline and its pharmaceutically acceptable acid addition salts.

14. 5-(4-pyridyl)-2,3,5,6-tetrahydro-imidazo[1,2-c]quinazoline-5-acetic acid ethyl ester and its pharmaceutically acceptable acid addition salts.

15. 6-phenyl-6-(4-pyridyl)-3,4,6,7-tetrahydro-2H-pyrimido[1,2-c]quinazoline and its pharmaceutically acceptable acid addition salts.

16. 6-phenyl-6-(2-pyridyl)-3,4,6,7-tetrahydro-2H-pyrimido[1,2-c]quinazoline and its pharmaceutically acceptable acid addition salts.

17. 6-(4-methylphenyl)-6-(4-pyridyl)-3,4,6,7-tetrahydro-2H-pyrimido[1,2-c]quinazoline and its pharmaceutically acceptable acid addition salts.

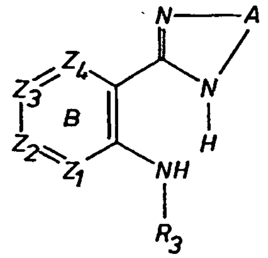
18. 6-(4-chlorophenyl)-6-(4-pyridyl)-3,4,6,7-tetrahydro-2H-pyrimido[1,2-c]quinazoline and its pharmaceutically acceptable acid addition salts.

19. 6-(4-pyridyl)-6-(2-thienyl)-3,4,6,7-tetrahydro-2H-pyrimido[1,2-c]quinazoline and its pharmaceutically acceptable acid addition salts.

20. 7-ethyl-6-phenyl-6-(4-pyridyl)-3,4,6,7-tetrahydro-2H-pyrimido[1,2-c]quinazoline and its pharmaceutically acceptable acid addition salts.

21. A polyazaheterocyclic compound according to claim 1 substantially as described with reference to any of the Examples.

22. Process for the manufacture of compounds of the general formula I given in claim 1 in which R_1, R_2, R_3, Z_1, Z_2, Z_3 and Z_4 and A have the meanings given there and the ring B, as stated there, can be substituted, and their acid addition salts, characterised in that a compound of the general formula II



(II)

(II)

in which R_3, Z_1, Z_2, Z_3, Z_4 and A have the meanings given in claim 1 and the ring B, as stated there, can be substituted, or an acid addition salt of the same, is condensed with a ketone of the general formula III

$$R_1 - CO - R_2 \qquad \text{(III)}$$

in which R_1 and R_2 have the meanings given in claim 1, or a reactive functional derivative of the same, if desired lower alkyl is introduced as a radical R_3 into a compound of the general formula I in which R_3 represents hydrogen, and/or a resulting compound of the general formula I is converted into an acid addition salt or the compound of the general formula I is liberated from a resulting acid addition salt.

23. Process according to claim 22 substantially as described with reference to any of the Examples.

24. Compounds of formula I when produced by a process according to claim 22 or 23 and their addition salts.

25 Pharmaceutical preparations, characterised by a content of a compound of the general formula I according to any one of claims 1 to 28 or a pharmaceutically acceptable acid addition salt of the same, and at least one pharmaceutical carrier.

26. Pharmaceutical preparations, characterised by a content of a compound of the general formula I according to any one of claims 9 to 14, or a pharmaceutically acceptable acid addition salt of the same, and at least one pharmaceutical carrier.

25. Pharmaceutical preparations, characterised by a content of a compound of the general formula I according to any one of claims 15 to 20, or a pharmaceutically acceptable acid addition salt of the same, and at least one pharmaceutical carrier.

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AN 1982:217872 CAPLUS
DN 96:217872
TI Polyazaheterocyclic compounds and pharmaceutical compositions containing them
IN Frei, Jorg; Schweizer, Ernst
PA Ciba-Geigy A.-G. , Switz.
SO Eur. Pat. Appl., 57 pp.
CODEN: EPXXDW
DT Patent
LA German
FAN.CNT 1

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	GB 2082577	A	19820310	GB 1981-24650	19810812
	GB 2082577	B2	19840328		
	ES 504736	A1	19820516	ES 1981-504736	19810813
	DD 201594	C	19830727	DD 1981-232590	19810813
	CA 1173831	A1	19840904	CA 1981-383782	19810813
	DK 8103623	A	19820216	DK 1981-3623	19810814
	FI 8102518	A	19820216	FI 1981-2518	19810814
	NO 8102762	A	19820216	NO 1981-2762	19810814
	AU 8174092	A1	19820218	AU 1981-74092	19810814
	JP 57054186	A2	19820331	JP 1981-126873	19810814
	ZA 8105621	A	19820825	ZA 1981-5621	19810814
	HU 29190	O	19840130	HU 1981-2385	19810814
PRAI	CH 1980-6197		19800815		

AB Condensed pyrimidines I [X = C2-4 alkylene, alkenylene; R, R1 = (un)substituted aliph., arom., heteroarom.,; R2 = H, alkyl; R3R4 = butadienediyl, azabutadienediyl] were prepd. Thus 2-H2NC6H4CN was cyclized with H2NCH2CH2NH2 to give 2-(2-aminophenyl)-4,5-dihydro-1H-imidazole which was treated with 4-acetylpyridine to give II. III was similarly obtained by using H2N(CH2)3NH2 and 2-acetylpyridine. At 10 mg/kg orally in rats II caused a 20% decrease in blood sugar level. At 20 mg/kg orally in dogs III caused 392% of Na+ excretion of controls.

IT **81933-58-6P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation)
(prepn. and cyclization of, with benzoylpyridine)
RN 81933-58-6 CAPLUS
CN 4-Pyridinamine, 3-(1,4,5,6-tetrahydro-2-pyrimidinyl)- (9CI) (CA INDEX NAME)